American Journal of Diseases of Children

VOLUME 62 JULY 1941 NUMBER 1

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HEREDITARY FACTORS IN THE BLOOD DYSCRASIAS

PRESIDENT'S ADDRESS

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DETROIT

My choice of subject is not due to any conceit of myself as a geneticist. I confess cheerfully a gross ignorance of the intricate and amazing developments of experimental genetics, which have all at once converted the common fruit fly from a ubiquitous minor pest to one of the most important denizens of the experimental laboratory.

Unfortunately for the geneticist, Homo sapiens offers no such free field for scientific breeding experiments as does Drosophila. So far as actual collection of evidence goes, one is still limited to the time-honored method of studying family trees, though present day investigators do have an advantage over their predecessors in being able to check their observations with the results obtained in experimental genetic studies, by means which are sometimes most complex. To have to follow this seemingly somewhat unscientific method is not altogether displeasing to me, as I like to speculate on unsolved problems of disease and dislike being halted too often by rude demands for proved facts.

I have been interested for years in the blood dyscrasias, of which a large proportion have a definite hereditary background while for others the role of heredity is still a matter of surmise. In collecting information regarding this background, I have had in mind several questions the answer to which with regard to any given disorder might supply information of value from the etiologic, the clinical or the eugenic point of view, or even from all three. Some of these questions are as follows:

For a particular disease, how good are the evidences of hereditary transmission and of its type? If such evidences are not wholly satisfactory, how may one acquire more certain information? Is the view that some of the blood dyscrasias are "race limited" tenable? Is there such a thing as race-limited disease? How long a life has a mutation, how widely and how rapidly does it spread, and how important is it from

Read at the annual meeting of the American Pediatric Society, Hot Springs, Va., May 22, 1941.

the point of view of eugenics? Does the same mutation appear often? Do diseases which seem to have close resemblances have similar genetic origins? Or, to put the question another way, would dissimilarity of inheritance indicate difference in fundamental etiology? Do excursions into genetics offer any light on obscure etiologic problems? Does the genetic background of a disease contribute anything to its clinical management?

Before taking up individual disease conditions in pursuit of answers to these questions, I should like to make one assumption as a basis for discussion. Nobody knows just what a gene is, but one of the current theories seems plausible enough and fits known facts well enough, I think, to warrant my assuming its approximate correctness for the present purpose. This theory is that the gene is a highly complex protein molecule and mutations are a result of rearrangement of outlying radicles of this molecule. Some rearrangements take place more readily than others and are more common. Some are less stable and hence less enduring. Experimental genetics has shown that reversal of mutations may, and does, occur.

In examining various diseases for answers to the questions posed, one would naturally begin with the condition whose heredity has been most thoroughly studied and is best known. This is unquestionably hemophilia. It is a striking disease, easily recognized, and its sex-linked heredity is generally understood, with the exception of the perennial question regarding female hemophiliacs. It is not impossible that female children with true hemophilia could be born of the rather unlikely mating of a male hemophiliac and a female carrier of the disease. The lack of such offspring of the few such matings recorded is often assumed to indicate that the trait under these conditions may be lethal.

Hemophilia offers an answer to the questions regarding the life of mutations and the possibility of repetition. The family trees of more than 250 hemophilic families have been studied. Some of them are long and some short. It is unlikely that all the strains developed from the same stem. Geneticists have some sort of mathematical legerdemain by which, given adequate data, they can calculate the probable frequency of a particular mutation. Haldane computed this for hemophilia and arrived at the figure of 1 in 100,000 generations. Put in another way, this means that in 1 generation there would be a new mutation for every 100,000 matings. There are special factors which probably tend to make this mutation of short duration. The severity of the disease and the short life of the hemophiliac result in both natural and artificial selection, but the fact that the character for the disease is a recessive carried by females leads to the frequent concealment of the trait for a generation or two, after which it appears in some unexpected quarter.

Genetically speaking, the sex-linked character of hemophilia separates it definitely from most of the other blood disorders. Sex-linked heredity of disease is not uncommon, but I know of only one other disorder of the blood which shows it. This is an anemia with elliptic cells, of which I shall speak shortly. It seems to me a logical inference that diseases the inheritance of which is dependent on genes located in different chromosomes may have their primary effects on different tissues. Current theory regarding the clotting mechanism suggests that the defect in hemophilia is located in the plasma, in which case one need not assume any such connection with the reticuloendothelium as seems evident in a number of the other dyscrasias.

I come next to three conditions which clinically and genetically form a fairly definite group and can well be considered together. They are congenital hemolytic icterus, elliptocytosis and the sickle cell trait. Elliptocytosis has been reported a number of times in this country and has been generally looked on as a curiosity with no special pathologic interest. More recently, however, several reports have appeared which indicate a not uncommon association of the trait with a disease state which parallels hemolytic icterus almost exactly with the single exception of the substitution of the elliptic cell for the spherocyte. On the other hand, the frequent occurrence of the trait without symptoms and the resemblance of the elliptic cells to those of the sickle form suggest a relation between the three conditions. There are, of course, definite differences. Heredity is dominant in all three, and a number of hematologists have expressed the belief that the cells do not take on their peculiar shape until they reach the reticulocyte stage. This might indicate that the mutations occur in the same gene.

The question of elliptocythemia has become involved recently by reports of more than one type of anemia in which a high proportion of elliptic cells are present. My associates and I at present are studying an anemia, new to us, which has had a high fatality rate in the affected family. The disease is characterized by the presence of many elliptic cells, and there is a clear history of sex-linked inheritance similar to that in hemophilia. We have observed a case of idiopathic hypochromic anemia in which the cell picture was practically identical with that of this hereditary disorder but there was no history of heredity. There have been several recent reports from Italy of cases of anemia in which the blood picture was similar, but there was no evidence of heredity and usually there was an increased resistance of the cells and wide resistance span. I believe that the elliptic cells in such conditions are really an unusual type of poikilocyte, which is not congenital and not to be confused with the hereditary cell form, as is done in much of the literature.

Hemolytic icterus, thanks chiefly to the extensive material at the disposal of Gänsslen, has been thoroughly studied as to the characteristics of its heredity, and the results offer some suggestions for the

study of less familiar diseases. While the disease trait is clearly a simple dominant and one of the parents must therefore be affected, Gänsslen has found that the parental disease may be so mild as to be revealed only by careful hematologic study. This fact has a definite clinical implication. There is a type of symptomatic hemolytic anemia, perhaps properly classified with Lederer's anemia, in which spherocytosis and increased fragility may be found. It is transient and susceptible to treatment. A patient with the disease should not, therefore, be subjected to splenectomy. In a doubtful case, if hematologic study of both parents reveals no evidence of a hereditary factor reasonable time should be allowed for the disappearance of the abnormalities in the blood before operation is advised.

Though there is now sufficient ground for belief in the heredity of Mediterranean anemia, there are not yet enough well studied pedigrees to make classification of the trait for the disease possible. Without taking time to analyze the evidence, I may say that I think it is probably a simple dominant, though recessivity has been suggested and some more complicated heredity cannot definitely be ruled out. The mild types are so difficult to recognize that they may easily be missed. Clinical observation seems to me to favor the idea that this disease is primarily a disturbance of some metabolic function, with a secondary effect on the marrow and the reticuloendothelium, and personal observations on the blood of infants with an early stage of the disease indicate that most, at least, of the peculiarities of the erythrocytes are not seen in the first stages. These observations are similar to those made in cases of the sex-linked elliptocytic anemia, which rather strikingly resembles the Mediterranean disease. It is obvious that the mutations for the two cannot lie in the same chromosome, as there is no suggestion of sex linkage in Mediterranean anemia.

Mediterranean anemia offers a good text for discussing the question of race-limited disease, which has been rather generally accepted both for this disease and for sickle cell anemia. My own opinion is that there is no such thing. When a disease-producing mutation takes place, it is evident that it will recur first in the neighborhood of its origin. If this is an isolated community, where there is a good deal of inbreeding, it will have a strong local foothold before it begins to appear in neighboring communities. It will be limited to a community, a province or a race in proportion to the clannishness and the isolation of the people involved. Furthermore, the mutations which gave rise to the sickle cell trait in Negroes and to Mediterranean anemia in Greeks and in Italians must have occurred many generations ago to have appeared as widely as they have among these peoples. This does not, however, constitute a reason for supposing that a proved case of sickle cell anemia in a Peloponnesian or of Mediterranean anemia in a Chinese child in Hawaii must be ascribed to an unlikely racial cross. In view of the present knowledge

about the repeated appearances of mutations, it is only common sense to explain such occurrence as new appearance of the mutations, which may, of course, set up new foci of the diseases. I have found reports of just one well established disease, an anomaly of the skin, all cases of which can be traced to a single ancestor. The differences in the hereditary makeup of races depend, of course, largely on an accumulation of genic variants in each racial group, and it is not improbable that in some groups this accumulation has resulted in an instability of certain genes and an increased susceptibility to mutations involving special tissues. The frequency of reports from Italy of cases of diseases of the spleen, the liver and the bone marrow has led me to wonder whether such an instability of some genes in the Italian people might not be inferred.

The problem of heredity in pernicious anemia is more complicated than in the diseases which I have been discussing, and in spite of the intense study the disease has received this problem is by no means completely worked out. There is ample evidence of an unusually high incidence in certain families to indicate that there must be a hereditary factor. There is also evidence that gastric anacidity is likewise common in such families, and possibly with it a lack of Castle's intrinsic factor. It is a curious fact that idiopathic hypochromic anemia also is associated with heredity of this type and that both it and pernicious anemia may develop in the same family and even, at different times, in the same patient. To confuse the issue further, gastric cancer occurs in such families with suspicious frequency. The difficulty with studying the heredity of these conditions is that since the diseases become manifest in adult life it is not easy to investigate the patient's antecedents or to obtain adequate studies of apparently healthy relatives. The result is that one may still choose among several theories, ranging from that of inherited gastric inferiority, which permits environmental factors to cause the disease to develop, to the flat-footed statement that the same mutant gene is responsible for all three diseases, again with environmental aid, or the rather timid suggestion that two genes may be involved, one affecting the stomach and the other the marrow. So far as pernicious anemia is concerned, there is not much doubt that anacidity and probably an absence of the intrinsic factor are often its hereditary precursors. Enough data are not available to determine whether the trait for pernicious anemia is dominant or recessive. It does not seem to be sex linked.

I had hoped in my perusal of the literature to find something really interesting about heredity in the thrombopenic purpuras. The whole subject of the purpuras is notoriously confused, clinically and etiologically as well as genetically. There are to be found in the literature a number of instances of hereditary purpuric tendencies in which the thrombopenic factor is not evident and in which the pedigrees are so

brief as to suggest a mutation of short duration. Glanzmann seems to have made out a good case for his hereditary thrombasthenia, but the trait, a simple dominant, is apparently rare. There are records, also rare, of the development of hemorrhagic thrombopenia in infants born of mothers similarly affected. If one substitutes platelets for red corpuscles, there is a striking parallelism between the clinical pictures of chronic or recurrent thrombopenia and hemolytic icterus. If a corresponding likeness in heredity were also evident, it might help to clarify some moot points regarding the interrelations of the spleen, the bone marrow and the blood vessels and might occasionally aid in a difficult clinical decision. I have been disappointed in finding no evidence of heredity in idiopathic thrombopenia. The lack of such evidence is not positive proof that a mutant for the disease does not exist. If it were recessive, in so rare a disorder it would hardly be apparent unless the condition were found to be established in some isolated area where consanguineous marriage is frequent.

I have not yet tried to answer one or two of the questions which I put at the beginning of this paper. Perhaps the most important is that concerning the frequency of particular mutations and the extent and rate of their occurrence. I have intimated in discussing hemophilia that that mutation is relatively frequent and often of short duration. There is no definite information on these points in other dyscrasias, except what may be gathered from the number and the length of disease pedigrees. Evidently several factors affect the extent of the occurrence and the duration of a variant. The degree of isolation of the community in which it arises is of course important. So is the relative severity of the disease process. If the disease is frequently fatal, it constitutes a limiting factor, especially if the variant is dominant. The sex-limited recessives are not so greatly affected in this way. Every mutation causing disease tends to racial degeneration. The more severe its effects, however, the more probability there is of the extent of its occurrence being decreased both by natural and by artificial selection. There is a definite tendency to reversion in a number of the mutations occurring in experimental organisms, and reversion may well occur frequently in man. The so-called "wild-type," or normal gene, is much more stable than its mutant descendants. Haldane has applied his mathematical magic to the problem of the number of generations required for an unhindered mutation to affect all possible subjects. His figure for an autosomal dominant or recessive is roughly 350,000 generations. It is evident that the visible effects of a dominant mutant will be manifested much more widely and rapidly at first than those of a recessive trait, which is clinically effective only in the homozygous state. Equality between the two types will be reached only after many thousands of generations. For sex-linked and sex-influenced traits the figure is much less. In the

case of severe disease Haldane's figures would probably be multiplied many times. An example may be found in the relative frequency of occurrence of hemophilia and color blindness, both sex-linked recessives. All things considered, I doubt whether Caminopetros' vision of the Greek race's being some day wiped out by erythroblastic anemia need be taken too seriously, even if one could eliminate Hitler from the picture.

In those conditions in which the factor inherited is the susceptibility to a disease which is activated to the pathologic state by environmental factors, here is an obvious opportunity for prophylaxis if the condition is well enough understood. This seems possible with regard to pernicious anemia, and some knowledge of the exciting factors in hemolytic icterus and sickle cell anemia is available. These disorders and others of more obscure etiology should repay further study.

I should like to be able to offer proof that similar disease effects arise from mutations in the same gene—or at least in the same chromosome—and that mutations in different chromosomes produce their primary effects on different tissues. Such suggestions at present are no more than speculative and with regard to diseases in man the proof is certainly a long way from adequate.

I have barely touched once or twice on the possible implications of applying the knowledge gained through eugenics to the problem of hereditary disease. That science has made considerable strides since its beginnings, and I know of no better place for its further development than in the minimizing of hereditary disease. Possible applications to the disorders I have been considering are so obvious, however, that I need not enumerate them.

This has been a rambling, not too scientific discussion. It was prepared not as a catalog of diseases but as an attempt to bring out and illustrate one point that has impressed me, that is, that most physicians have given too little attention to medical genetics. Family trees might be put to better use by the geneticist than by the genealogist. It is the part of the physician to collect in proper form the material for study and, I think, to see that the next generation of physicians has a clearer understanding of the interpretation of such material. Clinicians and geneticists must always consider problems from widely different viewpoints, and neither group can take over the other's function. There are evident reed and opportunity for collaboration.

DISCUSSION

Dr. Alfred H. Washburn, Denver: I am sure that every one has found this paper thought provoking. I have felt for some time that in the teaching of medical students the importance of study in the field of genetics is not sufficiently stressed.

Of course, my work has been with the so-called normal, or healthy, child, and I have been tremendously impressed with the increased understanding genetics has brought of the differences among equally healthy infants and children; so I am particularly appreciative of Dr. Cooley's work with children with various diseases.

DR. RUSTIN MCINTOSH, New York: I should like to ask the president two questions. First, it seems to me that his omission of a discussion of leukemia was conspicuous, because in the British literature a good deal is made of the genetic factor in leukemia. Will Dr. Cooley say something about that disease? Second, what did he find out in his study of Mediterranean anemia about the frequency of marriages of cousins, which are one of the sources for discovering recessive traits?

DR. THOMAS B. COOLEY: I shall answer Dr. McIntosh's second question first, because I know something about that. Marriage of cousins apparently is common in the families in which Mediterranean anemia occurs. Wintrobe studied the family trees of two families in an Italian colony in Baltimore, and while he did not mention the subject in the paper which he published on the study about a year ago, in a letter to me he stated that there seemed to be close in-breeding in the whole little Italian community and that the families were closely related. In Caminopetros' study in Athens and in some of the other family trees that have been studied there seemed to be rather strong evidence of interrelationship. I think that is a rather important factor.

Another thing revealed by study of diseases presenting evidence of heredity is that both parents of an affected subject may exhibit definite evidence of the disease, which would not occur with an ordinary recessive trait. In such cases it seems probable that each parent has a dominant trait in a rather mild form, and that would indicate that there is a good deal of consanguineous marriage among such persons. I have no doubt that is so, because all the regions where much Mediterranean anemia has occurred—and knowledge of a number of such districts is now available—are definitely isolated, even in the particular country where they are located.

As to leukemia, I know there is a good deal of discussion on heredity in leukemia, but I have not yet studied that question.

DR. GEORGE M. GUEST, Cincinnati: Dr. Cooley, may I add a question with regard to the significance of certain characteristics of the cells in Cooley's anemia? Various people have noted that the red blood cells of certain apparently unaffected members of a family in which there are cases of Cooley's anemia may be highly resistant to hemolysis without there being any erythroblasts in the circulation. Is such increased resistance a concomitant circumstance, or is it a characteristic linked with the evolution and the mutations of the disease?

DR. THOMAS B. COOLEY: I wish I could answer that question. I suppose you know that several investigators have expressed the belief that the target cell is the cell especially responsible for the increased resistance and the wide resistance span, and I rather accepted that idea until recently, when I saw several patients who had a wide resistance span, but no target cells. As for any such cell's having a specific relation to Mediterranean anemia, it certainly does not. Target cells occur frequently in the blood of persons with sickle cell anemia and apparently have the same effect in that disease, because an increased resistance of the red cells is a common feature of sickle cell anemia. So the target cell cannot bear a specific relation to Mediterranean anemia. However, it is true that if a patient with this disease has target cells in his blood it is not unknown to find target cells in the blood of his collateral relatives who have no obvious signs of disease but do have the wide resistance span. Caminopetros in his monograph took that as the chief evidence of a hereditary tendency to the disease in the persons he studied. As I have indicated, I am a little skeptical about that since seeing the patients whose blood did not contain target cells but whose red cells had a wide resistance span.

IMMUNITY TO TETANUS INDUCED BY COMBINED ALUM-PRECIPITATED DIPHTHERIA AND TETANUS TOXOIDS

BASED ON A STUDY OF ONE HUNDRED AND EIGHTY-SIX ALLERGIC CHILDREN

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To the pediatrician the problem of prophylaxis against tetanus is of particular importance. One half of the deaths from tetanus occur among children under 15 years of age. Tetanus may develop after receipt of a superficial scratch and even in persons lacking objective evidence of an injury for which no medical attention was sought. The routine injection of antitoxin in all cases of injury, a procedure carried out in the accident rooms of many hospitals and elsewhere, is obviously a dangerous practice when applied to allergic persons, especially those hypersensitive to horse dander, horse serum or both. The frequency of anaphylactic (allergic, hyperergic) shock among hypersensitive persons following the injection of serum is much higher than the reported incidence of 1 instance per 50,000 injections of serum in unselected cases. Numerous examples illustrating the inadequacy of passive immunization of soldiers against tetanus were furnished during the World War of 1914-1918.[1] Similar occurrences have been encountered in civil and industrial practice.[2] It is also of interest that there are apparently no persons who have a natural immunity to tetanus analogous to the natural immunity to diphtheria possessed by some; so tetanus antitoxin is not present in measurable amounts in the blood of normal subjects before

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2. Wolff-Eisner, A., and Jahr, J.: Failure of Tetanus Antitoxin in Animal Body, Deutsche med. Wchnschr. **53**:107 (Jan. 14) 1927. Măcelaru, T.: Tetanus Occurring After Preventive Injection of Antitetanic Serum, Case, Bucureşti med. **6**:146, 1934. Fanquez: Death of Patient in Spite of Preventive Use of Tetanus Antiserum, Ann. de méd. lég. **17**:801 (July) 1937. Hertz, J.: Failure of Tetanus Prophylaxis, Ugesk. f. læger **100**:871 (Aug. 4) 1938. Dietrich, H. C.: Tetanus in Childhood, with Special Reference to Treatment. Am. J. Dis. Child. **59**:693 (April) 1940.

vaccination,[3] notwithstanding the observations to the contrary reported by Ten Broeck and Bauer [4] and Gold.[5] The need for active immunization of allergic children against tetanus is obvious.

The capacity of the body to generate specific antitoxins after the simultaneous injection of several antigens has been demonstrated by numerous observers.[6] The use of a combination of diphtheria and tetanus toxoids seems to be advantageous in increasing the protection against both diseases, as compared with the protection obtained when either is given alone, without additional effort, but in children its practical value in prophylaxis against tetanus will be apparent only when it is employed on an extensive scale.

The literature is replete with reports on the efficacy of active immunization of human subjects with tetanus toxoid, plain or alum precipitated, but they deal largely with adults. The number of allergic children given injections of combined alum precipitated toxoids who have been reported on is too small to permit a comparison with my series of children. There are certain phases of the problem of vaccination of children with tetanus toxoid which require further investigation in detail. My purpose in the study reported on in this paper was to determine

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3. Lincoln, E. M., and Greenwald, C. H.: Active Immunization of Human Beings with Tetanus Toxoid, Proc. Soc. Exper. Biol. & Med. **30**:1241 (June) 1933. Sneath, P. A. T.: Development of Tetanus Antitoxin Following Administration of Tetanus Toxoid, J. A. M. A. **102**:1288 (April 21) 1934. Bergey, D. H., and Etris, S.: Immunization of Humans with Alum Precipitated Tetanus Toxoid, Am. J. Pub. Health **24**:582 (June) 1934. Acquired Natural Immunity Against Tetanus, Foreign Letters (Paris), J. A. M. A. **106**:1673 (May 9) 1936. Lahiri, D. C.: Absence of Specific Antitoxin in Persons Exposed to Risk of Infection, Indian J. M. Research **27**:581 (Oct.) 1939.

4. Ten Broeck, C., and Bauer, J. H.: Studies on the Relation of Tetanus Bacilli in the Digestive Tract to Tetanus Antitoxin in the Blood, J. Exper. Med. **37**:479 (April) 1923.

5. Gold, H.: Studies in Tetanus Toxoid: I. Active Immunization of Allergic Individuals with Tetanus Toxoid, Alum Precipitated, Refined, J. Allergy **8**:230 (March) 1937; On the Value of a "Repeat" Injection of Tetanus Toxoid (Secondary Stimulus) in Active Immunization Against Tetanus, J. Lab. & Clin. Med. **25**:506 (Feb.) 1940.

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(1) the minimum number of doses of alum-precipitated diphtheria and tetanus toxoids required to immunize all of the allergic children studied against tetanus, (2) the influence of the interval between two doses of toxoid on the antitoxin response and on the duration of immunity, (3) the relation of antitoxin response to age and sex, (4) the time of appearance of the maximum and adequate antitoxin response after two doses of toxoid, (5) whether active immunization could be applied to the allergic child without subjecting him to an undesirable general reaction and (6) whether one or more components of the alum-precipitated toxoid preparation would engender sensitization.

MATERIAL AND METHODS

This study is based on the results obtained with 186 children suffering from asthma, hay fever or allergic rhinitis. The ages ranged from 3 to 15 years. The preparation of combined alum-precipitated diphtheria and tetanus toxoids was injected subcutaneously in two doses of 0.5 cc. each at intervals of from one to ten months. With few exceptions, the patients were also given injections of pollen and other antigens during the entire period they were under observation.

The tetanus toxin employed in the preparation of the combined alum-precipitated diphtheria and tetanus toxoids contained 30,000 minimum lethal doses of toxin, which means that 1 cc. of a 1:30,000 dilution of the toxin injected subcutaneously would kill a guinea pig weighing 300 Gm. within ninety-six hours.

In this communication only the tetanus antitoxin titers, expressed in American units, are reported.

LEVELS OF ANTITOXIN WHICH INDICATE IMMUNITY TO TETANUS

Gold [5] assumed that to be of value active immunization against tetanus must produce an antitoxin titer at least equal to that present in the blood after passive immunization with a prophylactic dose of 1,500 American units of tetanus antitoxin. The minimal or critical protective value was arbitrarily placed at 0.1 unit of antitoxin per cubic centimeter of serum. After 1,500 units of tetanus antitoxin is injected into a person as a prophylactic, the serum of that subject will contain from 0.1 to 0.25 unit of antitoxin per cubic centimeter, but this is the maximum level reached on about the third day and most of the antitoxin has been lost by eleven days after injection. The incubation period of tetanus is between seven and fourteen days. However, the antitoxin titer from seven to fourteen days after passive immunization is more frequently below than above 0.1 unit per cubic centimeter, and since one prophylactic dose of 1,500 units of tetanus antitoxin is generally accepted as conferring adequate protection against tetanus, except in those cases in which the incubation period is prolonged, one should not consider a person to be inadequately protected against tetanus who after active immunization with at least two doses of alum-precipitated toxoid has

an antitoxin titer of less than 0.1 unit. Moreover, there is no scientific evidence to show that 0.1 unit of tetanus antitoxin per cubic centimeter of serum is necessary to protect an actively immunized human subject against tetanus.

Jones [7] found that 50 American units of antitoxin will protect an actively immunized guinea pig weighing 30 Gm. against a dose of live tetanus spores, while 1,200 American units of antitoxin, or 24 times as much, would be required for passive immunity. According to these results, while 0.1 unit of antitoxin per cubic centimeter of serum would be required for the passive immunization of human subjects, only one twenty-fourth of that, or approximately 0.004 unit, would be required when immunity was produced actively. Ramon [8] claimed that enough antitoxin to neutralize 1 minimum lethal dose of toxin (which equals 0.001 unit) will give protection to horses, which are highly susceptible to tetanus. Ramon [9] stated that an antitoxin level after active immunization against tetanus equal to 0.02 international unit per cubic centimeter was satisfactory. It should be borne in mind that the international unit is half of the U. S. P. unit. An antitoxin level of approximately 0.01 unit per cubic centimeter of serum, according to Sneath, Kerslake and Scruby,[10] appears to be the critical level desirable of attainment in the active immunization of the guinea pig. Judging from these and other reports, one may, with reasonable assurance, accept 0.01 unit of antitoxin per cubic centimeter of serum obtained through active immunization as the critical or protective level against tetanus in man, and that level was so regarded in this study. Any value less than 0.01 unit per cubic centimeter was designated as inadequate or nonprotective.

Unfortunately, there is no simple test for immunity to tetanus comparable to the Schick test for immunity to diphtheria, and the production of antitoxin must be studied by testing the blood serum of immunized subjects. In this study specimens of blood were obtained at varying intervals up to twenty-six months after the second injection of toxoid. The total number of antitoxin titrations performed was 656. Examination of these data revealed that the small number of patients who failed to attain an adequate antitoxin level were among those to whom injections were administered at intervals ranging from one to four months. All of another group of children to whom injections were

7. Jones, F. G.: Personal communication to the author.

8. Ramon, G., cited by Gold.[5]

9. Ramon, G.: Combined (Active-Passive) Prophylaxis and Treatment of Diphtheria or Tetanus, J. A. M. A. **114**:2366 (June 15) 1940.

10. Sneath, P. A. T.; Kerslake, E. G., and Scruby, F.: Tetanus Immunity: Resistance of Guinea Pig to Lethal Spore Doses Induced by Active and Passive Immunization, Am. J. Hyg. **25**:464 (May) 1937.

given at intervals ranging from five to ten months had an adequate antitoxin response. Thus, the division of the children in this series into these two groups afforded the opportunity to study more closely the antitoxin response after the second injection of the preparation of combined alum-precipitated toxoids.

RELATION OF ANTITOXIN RESPONSE TO SEX AND AGE

An analysis of the initial maximum titers ranging from 0.003 to 1 unit or more, of tetanus antitoxin per cubic centimeter of blood serum, following two doses of the preparation of combined alum-precipitated

TABLE 1.—*Relation Between Age and Maximum Initial Tetanus Antitoxin Titer of One Hundred and Eighty-Six Allergic Children After Immunization with Two Doses of Combined Diphtheria and Tetanus Toxoid*

Age, Years	Patients		Titer, Units of Antitoxin per Cc. of Blood Serum															
			0.003		0.01*		0.025		0.05		0.1		0.2		0.5		1 to 5	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Injections at Intervals of 1 to 4 Months																		
3- 6.....	19	13	0	0	1	5	1	5	2	10.5	6	32	6	32	2	10.5	1	5
7- 9.....	46	31	3	7	3	7	1	2	7	15	6	13	12	26	11	23	3	7
10-12.....	43	29	3	7	1	2	0	0	3	7	4	9	20	47	4	9	8	19
13-15.....	41	27	4	10	1	2	4	10	6	15	8	19	11	27	4	10	3	7
Total.....	149	100	10	7	6	4	6	4	18	12	24	16	49	33	21	14	15	10
Injections at Intervals of 5 to 10 Months																		
3- 6.....	2	5	0	0	0	0	0	0	0	0	0	0	0	0	1	50	1	50
7- 9.....	8	22	0	0	0	0	0	0	0	0	2	25	1	13	2	25	3	37
10-12.....	16	43	0	0	2	13	0	0	1	6	2	13	6	37	1	6	4	25
13-15.....	11	30	0	0	1	9	0	0	1	9	1	9	3	27	2	19	3	27
Total.....	37	100	0	0	3	8	0	0	2	6	5	14	10	26	6	16	11	30
Grand total..	186	100	10	5.4	9	4.8	6	3.2	20	10.8	29	15.6	59	31.7	27	14.5	26	14

* In this and in subsequent tables, patients with an antitoxin level of 0.017 unit per cubic centimeter are included with those who had a value of 0.01 unit.

toxoids administered to 118 boys and 68 girls showed no relation between sex and the antitoxin response.

It can be seen from table 1 that the percentages of children of the preschool and school age who were given injections of the combined alum-precipitated toxoids at intervals ranging from one to four months and who acquired an adequate initial antitoxin titer were 100 and 92, respectively.

The children of all ages given injections of alum-precipitated toxoids at intervals ranging from five to ten months responded with adequate antitoxin levels. Moreover, there was a definite increase in the antitoxin levels of this group of children as compared with those of the group who were given injections at intervals ranging from one to four months.

The percentages of children in the two groups who attained the highest antitoxin level (0.5 to 1 plus unit per cubic centimeter of serum) were 30 and 10, respectively.

It may be concluded from the figures presented in table 1 that all children of preschool age acquire adequate levels of tetanus antitoxin after receiving two doses of combined alum-precipitated toxoids at intervals of from one to ten months, whereas the children of school age acquire protection only when given injections at intervals of from five to ten months.

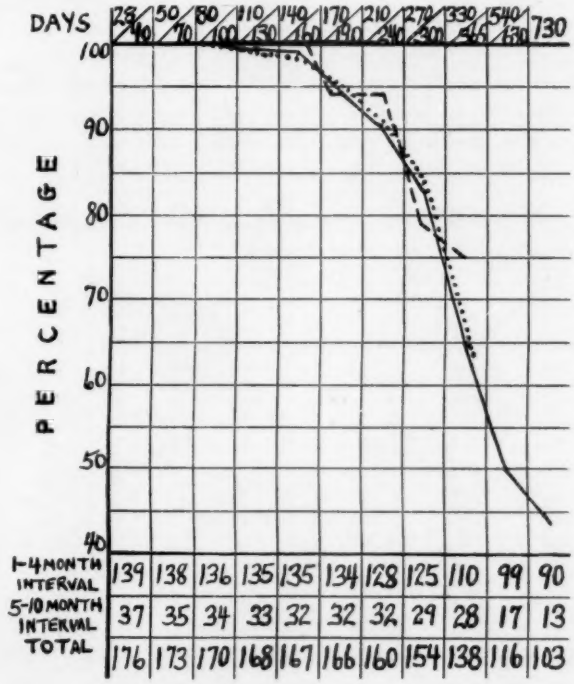
RATE OF DECLINE OF THE ANTITOXIN TITER FROM AN ADEQUATE TO AN INADEQUATE LEVEL

Of the 186 children, 176, or 94.6 per cent, acquired tetanus antitoxin titers above the critical level (0.01 unit per cubic centimeter of blood serum) within one month of receiving two doses of the combined alum-precipitated toxoids. The percentages of these 176 children who maintained adequate antitoxin levels for a varying number of days before the titer dropped from an initial adequate level to an inadequate one (0.003 unit) are shown in the chart. It was found that for a number of children once the antitoxin level dropped to 0.003 unit after the completion of active immunization it remained the same on subsequent tests, and there was evidence to show that this level was maintained for a long period. For this reason the antitoxin titer for all these children was recorded as being inadequate up to two years after the injection of the alum-precipitated toxoids.

Examination of the chart shows that all of the 176 children who were given injections of alum-precipitated toxoids at intervals of from one to ten months maintained adequate antitoxin titers for three months after receiving the injections. After four months the percentage of these children who had adequate immunity was 99.4, after six months 94.6, after nine months 83.1, after one year 65.4, after one and one-half years 50 and after two years 43.

An analysis to determine the influence of the length of the interval between the two doses of combined toxoids on the antitoxin response proved of interest but was carried out only for the children studied up to one year because of those given injections at intervals of from five to ten months too small a number were available for study at the end of one and one-half and two years to make a reliable comparison possible. One hundred and thirty-nine children were given injections at intervals of from one to four months and 37 at intervals of from five to ten months. Adequate antitoxin levels were maintained for three months by all the children of the former group and for five months by all those of the latter group. At the end of one year the percentages of children with

adequate immunity in the two groups were 63 and 75, respectively. While the percentages of the two groups of children who maintained adequate tetanus antitoxin levels after receiving combined alum-precipitated toxoids were not significantly different, the group given injections of toxoid at intervals of from five to ten months not only maintained higher adequate antitoxin levels longer but a larger percentage of them had titers of 0.1 to 0.2 unit per cubic centimeter at the end of one year. These observations will be emphasized later in another analysis (table 3).



1-4 MONTH INTERVAL	139	138	136	135	135	134	128	125	110	99	90
5-10 MONTH INTERVAL	37	35	34	33	32	32	32	29	28	17	13
TOTAL	176	173	170	168	167	166	160	154	138	116	103

Percentages of 176 allergic children who had achieved adequate immunity to tetanus (0.01 unit or more of antitoxin per cubic centimeter of blood serum) after receiving two 0.5 cc. doses of combined alum-precipitated diphtheria and tetanus toxoids who maintained adequate antitoxin levels for a varying number of days after immunization. The solid line represents the total number of children, the dotted line those given injections at one to four month intervals and the broken line those given the toxoids at five to ten month intervals.

TIME OF OCCURRENCE OF THE MAXIMUM INITIAL ANTITOXIN RESPONSE

In order to determine the time of occurrence of the maximum initial adequate antitoxin response after injection of the toxoids and the difference between the initial maximum antitoxin level and subsequent

levels, only those patients were selected for whom at least two titrations were done on specimens of blood obtained within one hundred days of receiving the combined toxoids. There were 30 patients in this category; essential data for them are recorded in table 2.

It will be observed from table 2 that for 17 of the 30 children initial antitoxin titers were obtained from seven to twenty-one days after injection of the toxoids. For 14 of these 17 children the initial levels proved to be the maximum levels, and the maximum antitoxin level

TABLE 2.—*Maximum Initial Antitoxin Titers for Thirty Patients and Titers Obtained Within One Hundred Days After Administration of Two Doses of Combined Alum-Precipitated Toxoid*

Initial Antitoxin Titer, Units per Cc. of Serum			Later Antitoxin Titers, Units per Cc. of Serum							
			After 21 Days		After 28 to 40 Days		After 50 to 70 Days		After 80 to 100 Days	
No. of Days After Administration of Toxoid	Titer	No. of Patients	No. of Patients	Titer	No. of Patients	Titer	No. of Patients	Titer	No. of Patients	Titer
7	0.017	1	..	...	1	0.2	..	...	..	...
	0.05	1	..	...	1	0.05	..	...	..	...
	0.1	1	..	...	..	...	1	0.2	..	...
	0.2	2	..	...	1	0.2	1	0.2	..	...
	1.0	3	1	1.0	2	1.0	..	...	..	...
	2.0	2	1	1.0	..	...	1	0.2	..	...
	3.0	3	..	...	1	3.0	1	1.0	..	...
					1	5.0				
14	0.2	1	..	...	..	...	1	0.1	..	...
	0.5	1	..	...	1	0.2	..	...	..	...
21	0.1	1	..	...	1	0.1	..	...	..	...
	0.5	1	..	...	..	...	1	0.1	..	...
30	0.1	2	..	...	..	...	2	0.05	..	...
	0.2	3	..	...	..	...	..	...	1	0.01
									2	0.1
	0.5	3	..	...	..	...	2	0.2	1	0.2
	1.0	2	..	...	..	...	..	...	1	0.2
									1	1.0
60	0.025	1	..	...	..	...	..	...	1	0.01
	0.1	1	..	...	..	...	..	...	1	0.05
	0.2	1	..	...	..	...	..	...	1	0.05

was reached by 2 of the remaining 3 children in from twenty-eight to forty days and by 1 child in sixty days. In each instance the intial titer obtained thirty days after injection of the toxoids for 10 children proved to be the maximum titer. It therefore appears evident that the maximum initial adequate titer in the vast majority of cases appears from seven to thirty days after basic immunization with combined alum-precipitated toxoids. Moreover, all the subsequent titers obtained within one hundred days of injection of the toxoids dropped, with the exception of an identical titer in 1 instance and an increased titer in another, which was obtained only from fifty to seventy days after injection of the toxoids.

The limitation of the interval after injection of the toxoids to one hundred days was based on the observation that antitoxin titers after more than one hundred days in the large majority of instances showed an appreciable decline. In this connection it was noted from a study of 641 titrations performed for the 176 children who acquired adequate antitoxin levels (chart) that the titers of all but 7 children fell progressively from maximum initial levels. The titers of the latter group increased subsequent to a previous decline. For 5 of these 7 children the increase in titer was negligible, while for the remaining 2 the increase in titer to 0.05 unit per cubic centimeter occurred subsequent

TABLE 3.—*Maximum Initial Tetanus Antitoxin Titer of One Hundred and Thirty Allergic Children and Titers Obtained in Less than One Year, When the Titer Dropped to 0.003 Unit per Cubic Centimeter of Blood Serum, and One Year After Immunization with Two Doses of Combined Alum-Precipitated Diphtheria and Tetanus Toxoids After Injection of Toxoids*

Maximum Initial Antitoxin Titer, Units per Cc.	Patients		Antitoxin Titer, Units per Cc. of Serum After Injection of Toxoids													
			Less Than One Year		One Year											
			0.003		0.003		0.01		0.05		0.1		0.2		0.01 to 0.2	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0.017	3	2	2	67	1	33	0	0	0	0	0	0	0	0	0	0
0.025	4	3	2	50	2	50	0	0	0	0	0	0	0	0	0	0
0.05	17	13	9	53	3	18	4	23	1	6	0	0	0	0	5	29
0.1	19	15	6	32	4	21	6	32	3	15	0	0	0	0	9	47
0.2	44	34	5	11	5	11	27	62	5	11	1	2.5	1	2.5	34	78
0.5	22	17	1	5	1	5	8	36	8	36	2	9	2	9	20	91
1.0 and over	21	16	0	0	2	9.5	5	24	5	24	2	9.5	7	33	19	90
Total	130	100	25	19	18	14	50	38	22	17	5	4	10	8	87	67

to a previous decline to 0.017 unit. These data cannot be explained satisfactorily except on the basis of possible technical error occurring in the process of titration. The idea that a tetanus antitoxin response may be comparable to the diphtheria antitoxin response which occurred with an appreciable frequency in the children of this series as a result of exposure cannot at the moment be seriously entertained, since an acceleration of immunity in an actively immunized person or a natural immunity in a nonimmunized person following exposure to tetanus spores has yet to be proved.

Data are recorded in table 3 only for those patients whose blood serums were available for the first titration within one hundred days of receiving two doses of the alum-precipitated toxoids. Thereafter, for up

to one year after administration of the toxoids specimens of blood were obtained from these patients at various intervals. For the patients whose antitoxin titers dropped to the inadequate level (0.003 unit per cubic centimeter) before the end of one year there was no need to perform additional titrations because this level remained unchanged at the end of one year after receiving the toxoids. Thus, of the 186 children 130 were eligible for this phase of the study.

Of the 130 children given injections of alum-precipitated toxoids at intervals of from one to ten months, 42, or 33 per cent, showed a drop in antitoxin titer from an adequate to an inadequate level one year or less than one year after receiving two doses of combined alum-precipitated toxoids, while 88, or 67 per cent, had adequate antitoxin values, ranging from 0.01 to 0.2 unit per cubic centimeter of serum, a year after receiving the injections. It is noteworthy that all of the children who had maximum initial titers of from 0.017 to 0.025 unit of antitoxin per cubic centimeter after receiving the combined toxoids showed a drop in titer to the inadequate level (0.003 unit) one year later, while the percentages of children who showed a drop in titer to the inadequate level from initial values of 0.05, 0.1, 0.2 and from 0.5 to 1 unit or more of antitoxin per cubic centimeter of serum were 71, 53, 22 and 9, respectively. Moreover, only those children who had maximum initial titers of 0.2, 0.5 and 1 unit or more had values of 0.1 or 0.2 unit of antitoxin one year after receiving the combined toxoids, the percentages being 5, 18 and 43, respectively.

Of the 130 children for whom data are given in table 3, 103 were given two doses of combined alum-precipitated toxoids at intervals ranging from one to four months and 27 at intervals of from five to ten months. In each of the two groups 19 per cent of the children showed a decline in antitoxin titer from a maximum initial adequate level to an inadequate one less than one year after receiving the toxoids. The percentage of children having each of the antitoxin levels from 0.017 to 0.2 unit was approximately the same in both groups, while the percentage showing a fall in titer to the inadequate level progressively decreased as the initial antitoxin level increased. However, of the children with an initial level of 0.5 unit 5 per cent showed a drop in titer to the inadequate level and all of them had received injections of toxoid at intervals of from one to four months. All of the children in both groups with initial levels of 1 unit or more failed to show a drop in titer to the inadequate level until one year after receiving the toxoid. The drop in titer to the inadequate level occurred only in the children given injections of the toxoid at intervals of from one to four months; it occurred in 17 per cent of them. Moreover, 56 per cent of the children given the toxoid at intervals of from five to ten months, as compared

with 33 per cent of those receiving injections at intervals of from one to four months, had from 0.1 to 0.2 unit of antitoxin per cubic centimeter of serum at the end of one year. This ratio of almost 2:1 is largely due to the fact that 41 per cent of the children of the former group as compared with 17 per cent of those in the latter group had maximum initial titers of from 0.5 to 1 unit or more.

It can be concluded that the difference in antitoxin response between the children given injections at intervals ranging from one to four months and those given the toxoid at intervals of from five to ten months was that a significantly higher percentage of the children in the latter group attained the highest antitoxin levels within one-hundred days of active immunization, and one year later a higher percentage also showed values of 0.1 and 0.2 unit of antitoxin per cubic centimeter of serum (ratio of 2:1).

INFLUENCE OF A THIRD DOSE OF COMBINED ALUM-PRECIPITATED TOXOIDS ON THE ANTITOXIN RESPONSE OF CHILDREN WHO FAILED TO ATTAIN ADEQUATE PROTECTION AFTER RECEIVING TWO INJECTIONS

For 10, or 5.4 per cent, of the 186 children used in this study it has been recorded that at present they have failed to acquire adequate protection against tetanus after two doses of toxoid. It should be stated that the inadequate values of 0.003 unit of antitoxin per cubic centimeter of serum was determined once for 5 children and twice for 1 child. Moreover, all of these 10 children received the two injections at intervals of from one to four months, while all the children given injections at intervals of from five to ten months attained adequate protection. Thus, 10, or 6.8 per cent, of the 149 children who were given two injections of alum-precipitated toxoids at intervals of from one to four months failed to attain adequate protection. However, in the absence of any practical test for determining immunity to tetanus, the position is taken that tetanus antitoxin levels must be adequate in every case.

Of the 10 children who failed to acquire adequate protection after two doses of the combined alum-precipitated toxoids, 9 were given a third, or "stimulating," dose. All of them attained an adequate antitoxin level within one month of receiving the stimulating dose of toxoid. The antitoxin level of 1 patient was 0.017 unit per cubic centimeter of serum and for the other 8 the maximum titers ranged from 0.05 to 1 unit.

From the evidence presented in this paper, it appears that all allergic children who are given three doses of 0.5 cc. each of alum-precipitated toxoids at intervals of from one to ten months may be expected to acquire an adequate immunity to tetanus.

REACTIONS AND SENSITIVITY

Using a preparation of combined alum-precipitated diphtheria and tetanus toxoids for all children instead of tetanus toxoid alone serves the double purpose of providing protection against both diphtheria and tetanus. Besides, this type of vaccination reenforces the immunity to diphtheria of those children who have been previously immunized against the disease, either actively or naturally. Local or systemic reactions following the first dose of the preparation of combined toxoids can be attributed to increased sensitivity to diphtheria bacillus protein. Thus, an increased number of reactions may be expected to follow the second dose of the combined toxoids not only because of the greater risk of increased sensitivity to diphtheria bacilli but because of the added risk of sensitivity either to the tetanus bacillus protein or to the components of the toxoid preparation itself. If these undesirable reactions do occur, the advantages attributed to simultaneous active immunization may be nullified to some extent. However, no disturbing reactions were encountered among the children in my series. The type of reaction to a third or fourth dose of combined toxoids administered one or more years after the completion of a primary course of two doses is now being studied.

All injections of the combined alum-precipitated toxoids were given subcutaneously on the upper and outer aspect of the arm. Approximately 25 per cent of the children had local reactions of various degrees. In the majority of instances the reaction was mild, consisting of redness or slight swelling during the first forty-eight hours after the injection was given. Local reactions occurred with about equal frequency after the two doses. Owing to the presence of alum in the preparation, absorption was delayed. An indurated, painless nodule persisted for from one to four weeks or more. The alum content of the preparation of combined toxoids is somewhat less than that of the alum-precipitated diphtheria toxoid. Two children had an elevation of temperature to 103 F., which commenced in 1 child about six hours after the injection of the first dose and in the other after the second dose. The temperature was normal after one day. All of the reactions encountered were harmless.

A concentration of antigens or other substances contained in a given volume of a preparation intended for subcutaneous injection probably bears a closer causal relation to a local reaction in a person insensitive to a specific substance than any other factor. It may be expected that in a majority of instances injection of a 0.5 cc. dose of a preparation containing the same concentration of a substance as 1 cc. of another preparation will be followed by fewer and milder reactions than injection of 1 cc. of the second preparation. For example, an extracting fluid com-

posed of equal volumes of glycerin and a buffered solution can be standardized so that 10,000 noon units of ragweed pollen will be contained in 0.5 cc. of one extract and in 1 cc. of another extract. Nonspecific local reactions are more frequently encountered after the larger than after the smaller dose in persons sensitive to ragweed pollen. This result can be duplicated with corresponding volumes of alum-precipitated toxoids of the same antigenic potency. In children the need for using the smaller volume of a toxoid preparation, such as was employed in this study, without sacrificing potency is obvious.

Occasional reference is made in the literature to allergic general reactions following the administration of tetanus toxoid, and from a survey of articles which deal largely with the "normal" adult population it may be stated that allergic reactions are relatively uncommon, despite the fact that all persons received two and many received three injections of toxoid. Hall [11] reported that 2 of 47 patients had urticarial reactions after the second dose of toxoid (not alum precipitated). Gold [12] encountered only 1 nonallergic person among about 200 immunized with alum-precipitated toxoid during the last five years in whom urticaria developed shortly after the second injection of alum-precipitated toxoid. Parish and Oakley [13] described an anaphylactic reaction ending with generalized urticaria in a woman ten minutes after the second injection of plain tetanus toxoid. Scratch tests performed with 1 : 10 dilutions of the toxoid preparation and of Witte's peptone gave whealing reactions. Whittingham [14] gave 61,000 members of the Royal Air Force personnel two 1 cc. doses of tetanus toxoid (not alum precipitated) at an interval of six weeks. From ten minutes to one hour after the second injection there developed in 9 persons generalized urticaria, with or without a chill. Another 5 persons had generalized aches and pains and slight elevation of temperature from thirty minutes to an hour after the second dose of toxoid. Scratch tests showed positive reactions with Witte's peptone in some cases. Cooke and his associates [15] reported that of 25 patients given reinjections of tetanus toxoid (alum precipitated) at an interval of from two to four months after the first injection, in 3 sensi-

11. Hall, W. W.: Active Immunization Against Tetanus with Tetanus Toxoid, U. S. Nav. M. Bull. **35**:33 (Jan.) 1937.

12. Gold, H.: Active Immunization of Allergic Individuals by Means of Alum Precipitated Toxoid, J. Allergy **9**:545 (Sept.) 1938.

13. Parish, H. J., and Oakley, C. L.: Anaphylaxis After Injection of Tetanus Toxoid: Case, Brit. M. J. **1**:294 (Feb. 24) 1940.

14. Whittingham, H. E.: Anaphylaxis Following Administration of Tetanus Toxoid, Brit. M. J. **1**:292 (Feb.), 1940.

15. Cooke, R. A.; Hampton, S.; Sherman, W. B., and Stull, A. L.: Allergy Induced by Immunization with Tetanus Toxoid, J. A. M. A. **114**:1854 (May 11) 1940.

tization was induced, as evidenced by a positive cutaneous reaction to a scratch test performed with a 1:10 dilution of toxoid, up to eight months after the second dose, and another showed sensitization four months after the first dose. Only 1 of these patients had generalized urticaria ten minutes after the second dose of toxoid. The sensitivity in these allergic patients was induced by a proteose contained in the toxoid preparation.

Induced sensitiveness to the bacterial products of diphtheria bacilli has been reported by Neill and Fleming [16] and others and to the bacterial products of Clostridium tetani by Cooke and his associates.[15]

In my series of 186 allergic children not 1 child had a systemic reaction resembling in any way the known allergic syndromes after a second injection of the combined alum-precipitated diphtheria and tetanus toxoids. A large majority of these children had either been previously actively immunized or had acquired a natural immunity to diphtheria. Some or all of the extensive local reactions and the elevation of temperature in the 2 instances previously mentioned may be viewed with suspicion as being allergic reactions either to one or to all of the substances or to the proteose in the culture medium. Scratch tests with the undiluted combined alum-precipitated toxoids were performed on 114 of the children from two to thirty months after the second dose of toxoid. The results of these tests did not confirm the allergic nature of the local or febrile reactions if a negative reaction, immediate or delayed, is accepted as a criterion of insensitivity. However, the striking absence of positive reactions to the scratch test with the alum-precipitated toxoid preparation along with an incidence of local reactions not higher than that reported in the literature for adults suggests that such responses may be peculiar to children—nonallergic as well as allergic.

COMMENT

Bacteria are the most complex antigens in common use, and their antigenic structure is closely related to virulence and to all bacterial substances. Toxin is one of the products of bacteria to which an antigenic response may be provoked. The best and most durable immunity is that actively acquired, in which the body cells are stimulated and trained; as it were, to build up an effective defense against the offensive forces of an invading pathogenic substance. Thus, one of the most fundamental concepts of the role of allergy in bacterial immunization is the fact that once the cells of the body have come in contact with an antigenic substance they never again fear their original relation to that substance.

16. Neill, J. M., and Fleming, W. L.: Studies on Hypersensitiveness to Diphtheria Bacilli: I. An Immediate Skin Reaction Which Can Be Passively Transferred, J. Exper. Med. **44**:33 (Jan.) 1929.

Long after antibody production has ceased the cells remain in such a condition that contact with the antigen will stimulate them to produce antibodies more quickly and more abundantly than usual. Repeated injections are, on this account, more effective in raising the antibody titer to a higher level than a single injection even of a large dose.

A natural immunity to certain diseases is acquired through invasion by the pathogenic organism specific for the disease, and the advantages persist after recovery from the disease. Since a natural immunity against tetanus has not been demonstrated, the importance of the role of the first injection of toxoid in the establishment of an effectual immunity against tetanus cannot be overemphasized. The state of allergy can be induced even under unfavorable conditions at the time of vaccination. Ramon and Laffaille [17] pointed out in 1925 that when an injection of antitoxin into a guinea pig is supplemented by the simultaneous injection of toxoid in another part of the body the immunizing action of the toxoid is more or less hindered by the antitoxin. However, the first injection of toxoid had left an impression on the cells, for the animal could later be immunized by a second injection of toxoid alone. Similarly, tests made on soldiers showed that an active immunization against tetanus could be realized by the simultaneous injection of antitetanus serum and tetanus toxoid, followed by one or several doses of toxoid at intervals of two or three weeks.[18] Moreover, persons treated by serovaccination have the same antitoxin response to a subsequent dose of toxoid injected several months or a year later as do persons who have been vaccinated with toxoid alone.

In the absence of any practical test to determine immunity to tetanus, treatment with alum-precipitated tetanus toxoid must be depended on to induce adequate immunity in almost all, if not all, persons treated. In this study one dose of toxoid afforded protection of relatively short duration to less than one half of the children vaccinated, while a higher incidence was reported by McBryde.[19] Two doses effected immunity

17. Ramon, G., and Laffaille, A.: Immunization Against Tetanus, Compt. rend. Soc. de biol. **93**:582 (Aug. 14) 1925.

18. Ramon, G., and Zoeller, C.: Tetanus Toxoid and Active Immunization of Humans Against Tetanus, Ann. Inst. Pasteur **41**:803 (Aug.) 1927. Ramon, G.: New Methods in Combat Against Tetanus: Serovaccination, Serotoxoid Therapy, Prevention by Antitoxin Solutions, Bull. Acad. de méd., Paris **121**:609 (May 2), 1939. Sacquépée, E.: Immunization Against Tetanus by Simultaneous Use of Antiserum and Anatoxin, Paris méd. **1**:491 (June 3) 1933. Sacquépée, E., and Jude, A.: Degree and Duration of Immunity After Revaccination in Man Immunized by Simultaneous Application of Antiserum and Toxoid, Compt. rend. Soc. de biol. **125**:711, 1937.

19. McBryde, A.: Tetanus Immunization with Alum Precipitated Toxoid, South. M. J. **30**:565 (June) 1937.

in 176, or 94.6 per cent, of 186 allergic children, while the remainder acquired adequate protection after a third dose. Hence, from a clinical viewpoint it appears that to produce adequate immunity to tetanus in allergic children of all ages three doses of 0.5 cc. each of alum-precipitated toxoid (of a capacity of 30,000 minimum lethal doses per cubic centimeter) should be administered at intervals of at least one month.

SUMMARY AND CONCLUSIONS

Of 186 allergic children (118 boys and 68 girls) between the ages of 3 and 15 years who were given two injections of 0.5 cc. each of combined alum-precipitated diphtheria and tetanus toxoids, which had a tetanus toxicity of 30,000 minimum lethal doses per cubic centimeter, 149 were given the toxoids at intervals of from one to four months and 37 at intervals of from five to ten months. Antitoxin levels were determined at various periods after the second dose of toxoid was given; a total of 656 titrations was performed.

A discussion of the protective tetanus antitoxin level was presented to indicate the basis for accepting as critical or adequate for preventing tetanus in man a level of 0.01 unit per cubic centimeter of blood serum obtained through active immunization. Any value less than 0.01 unit of antitoxin was considered inadequate or nonprotective.

Local reactions were harmless. They occurred after the first and the second injection of toxoid in about 25 per cent of the children. Four to six hours subsequent to an injection 2 children experienced an elevation of temperature of about twenty hours' duration. No general (constitutional) reaction, such as urticaria or asthma, occurred.

All of the 114 children who were tested by the scratch method with the undiluted combined alum-precipitated toxoids reacted negatively to the various substances in the preparation. The tests were performed from two to thirty months after the completion of active immunization.

Sex played no role either in the incidence of the maximum initial adequate antitoxin response or in the duration of immunity in the various groups tested.

Of the 186 children, 176, or 94.6 per cent, had protective levels of tetanus antitoxin following two doses of alum-precipitated combined toxoids injected at intervals of from one to ten months. The 10 children, or 5.4 per cent, who had inadequate antitoxin levels (0.003 unit per cubic centimeter of blood serum) were given the toxoid at intervals of from one to four months. Nine of these 10 children were given a third, or "stimulating," dose of combined alum-precipitated toxoids, and within one month all of them had adequate antitoxin levels.

The children of preschool age acquired adequate immunity to tetanus after two doses of combined alum-precipitated toxoids injected at inter-

vals of from one to ten months, whereas the children of school age acquired protection only after receiving injections at intervals of from five to ten months.

The initial maximum antitoxin level was reached by almost all children in from seven to thirty days after they had received the toxoids.

All of the 176 children maintained adequate antitoxin levels for three months after receiving the toxoids. One year after receiving the combined toxoids 65.4 per cent of the children had adequate antitoxin titers (0.01 unit or more), and two years after being given the injections 43 per cent had protective antitoxin levels.

Of the 176 children, 139 were given injections of the combined toxoids at intervals of from one to four months and 37 at intervals of from five to ten months. A significantly greater percentage of the latter group had responded to the highest antitoxin values not only within one hundred days of receiving two doses of the combined alum-precipitated toxoids but one year after the immunization.

Thus, the intervals between the two doses of combined toxoids had a direct influence on the antitoxin response.

In the absence of any practical test to determine immunity to tetanus, alum-precipitated tetanus toxoid must be depended on to induce adequate immunity in the children treated. Since the development of active immunity against tetanus was influenced by the age of the patient and the interval between injections, it appears reasonable to state, on the basis of the results obtained in this study, that to insure adequate active protection against tetanus for all children treated three doses (of 0.05 cc. each) of alum-precipitated toxoid should be administered at intervals of at least one month.

Until a large number of children in this country have been vaccinated over a considerable period, despite the demonstration of the practical value of active immunization against tetanus, it is recommended that at the time of injury a third, or "stimulating," dose of alum-precipitated tetanus toxoid be given.

Finally, should exposure to tetanus occur before vaccination is completed and immunity is established (seven to thirty days) a simultaneous injection of antitetanus serum and toxoid (serovaccination) should be given.

F. G. Jones, of the Lilly Research Laboratories, gave technical assistance in this study.

Eli Lilly & Co. furnished the combined alum-precipitated diphtheria and tetanus toxoids used in this study.

450 West End Avenue.

ELECTROCARDIOGRAPHIC ALTERATIONS IN RHEUMATIC FEVER IN CHILDREN

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In patients with rheumatic fever the heart frequently is involved, and if manifestations in the joints are slight or absent the diagnosis of rheumatic fever may depend on the demonstration of the presence of cardiac involvement by physical examination or by laboratory methods, especially by the electrocardiographic examination. Considerable difference of opinion exists with regard to the frequency of abnormalities and of alterations in individual waves in the electrocardiogram of patients with rheumatic fever. In table 1 are assembled the electrocardiographic changes described in some of the larger series of reported cases.[1] The discordant results probably can be attributed to the stage of the disease

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1. (*a*) Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1-35 (Jan.) 1924. (*b*) Coombs, C. F.: Rheumatic Heart Disease, New York, William Wood & Company, 1924; cited by Reid and Kenway.[1f] (*c*) Swift, H. F.: Rheumatic Fever, Am. J. M. Sc. **170**:631-647 (Nov.) 1925. (*d*) Bain, C. W. C., and Hamilton, C. K.: Electrocardiographic Changes in Rheumatic Carditis, Lancet **1**:807-809 (April 17) 1926. (*e*) Rothschild, M. A.; Sachs, B., and Libman, E.: Disturbances of Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, Am. Heart J. **2**:356-374 (April) 1927. (*f*) Reid, W. D., and Kenway, F. L.: Value of Electrocardiogram in Acute Rheumatic Fever, New England J. Med. **198**:177-181 (March 15) 1928. (*g*) McMillan, T. M., and Cook, A.: The Electrocardiographic Changes Occurring During Rheumatic Fever, Atlantic M. J. **31**:806-812 (Aug.) 1928. (*h*) Shapiro, M. J.: Electrocardiographic Changes in Quiescent Rheumatic Diseases in Children, Am. Heart J. **5**:504 (April) 1930. (*i*) Weiss, M. M.: Electrocradiograms in Children with Chronic Heart Disease and Heart Failure, Am. J. Dis. Child. **42**:1339-1348 (Dec.) 1931. (*j*) Master, A. M., and Jaffe, H. L.: Rheumatoid (Infectious) Arthritis and Acute Rheumatic Fever, J. A. M. A. **98**:881-882 (March 12) 1932. (*k*) Drawe, C. E.; Hafkesbring, E. M., and Ashman, R.: Children's Electrocardiograms: II. The Changes in Children's Electrocardiograms Produced by Rheumatic and Congenital Heart Disease, Am. J. Dis. Child. **53**:1470-1484 (June) 1937. (*l*) Juster, I. R.: The Significance of Rheumatic Activity in Chronic Rheumatic Heart Disease: I. Intensity and Extent, Am. Heart J. **15**:1-21 (Jan.) 1938. (*m*) McGee, L. C.: The Electrocardiogram in Rheumatic Fever, South. M. J. **31**:480-483 (May) 1938.

TABLE 1.—*Electrocardiographic Alterations in Cases of Rheumatic Fever and Rheumatic Carditis Reported in the Literature*

Author	Year	No. of Patients	No. of Electrocardiograms	P Wave	PR Interval	QRS Complex	RST Segment	T Wave	QT Interval	Axis Deviation		Changes in Rhythm	No. of Patients with Abnormalities	Percentage of Patients with Abnormalities
										Right	Left			
Cohn and Swift [1a]	1924	37	2,591	..	31	20	..	..	..	4	14	22	35	95
Coombs [1b]	1924	79	.....	..	..	..	53	..	..	.	..	..	53	67
Swift [1c]	1925	81	.....	..	70	..	..	..	..	..	..	..	75	93
Bain and Hamilton [1d]	1926	50	50	..	2	1	3	2	..	2	1	1	11	22
Rothschild, Sachs and Libman [1e]	1927	65	Serial	..	23	35	45	25	..	..	..	..	61	94
Reid and Kenway [1f]	1928	26	281	..	24	..	21	..	..	..	..	11	26	100
McMillan and Cook [1g]	1928	43	Serial	23	22	14	14	11	.	..	..	10	36	84
Shapiro [1h]	1930	119	Serial	10	10	8	74	3	..	..	..	3	..	?
Weiss [1i]	1931	87	.....	..	26	..	7	2	..	44	..	1	..	?
Master and Jaffe [1j]	1932	63	Serial	8	41	19	53	25	.	2	7	23	36	100
Drawe, Hafkesbring and Ashman [1k]	1937	100	.....	..	8	17	5	10	25	16	10	..	40	40
Juster [1l]	1938	59	.....	..	14	51	16	13	..	..	..	27	53	90+
McGee [1m]	1938	50	.....	18	22	5	15	12	..	..	..	..	46	92
Orgain, Martin and Anderson..	1941	70	118	9	6	26	7	12	17	12	8	4	49	70

at which the tracing was taken, the frequency or absence of serial records and the variations in standard criteria for the determination of abnormality in a single electrocardiogram. The electrocardiogram is more likely to be abnormal during the acute stage of the disease or when the process in the heart is far advanced. The value of serial electrocardiographic studies in rheumatic fever has been clearly demonstrated by the investigations of Cohn and Swift,[1a] Rothschild, Sachs and Libman [1e] and Master and Jaffe.[1j] In spite of the many detailed studies of the electrocardiograms of normal children, there is disagreement with regard to the constituent features and the limits of variation in the normal electrocardiogram.[2]

It is the purpose of this paper to report the results of electrocardiographic studies on 70 children with rheumatic fever, aged 4 to 14 years, who were observed in a southern hospital, and to present criteria for the determination of electrocardiographic abnormality which, on the basis of reports in the literature,[3] and our own experience, we believe to be satisfactory.

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2. (*a*) Seham, M.: The Electrocardiogram in Normal Children, Am. J. Dis. Child. **21**:247-281 (March) 1921. (*b*) Lincoln, E. M., and Nicolson, G. H. B.: The Hearts of Normal Children: III. Electrocardiographic Records, ibid. **35**: 1001-1020 (June) 1928. (*c*) Perry, C. B.: Electrocardiograms of Normal Children, Arch. Dis. Childhood **6**:259-264 (Oct.) 1931. (*d*) McGinn, S., and White, P. D.: The Duration of the Q-R-S Complex in the Normal and in the Abnormal Electrocardiogram, Am. Heart J. **9**:642-654 (June) 1934. (*e*) Master, A. M.; Dack, S., and Jaffe, H. L.: Chest Leads in Normal Children, Proc. Soc. Exper. Biol. & Med. **32**:1529-1531 (June) 1935. (*f*) Levy, R. L., and Bruenn, H. G.: Precordial Lead of the Electrocardiogram (Lead IV) as Aid in Recognition of Active Carditis in Rheumatic Fever, Am. Heart J. **10**:881-888 (Oct.) 1935. (*g*) Robinow, M.; Katz, L., and Bohning, A.: The Appearance of the T Wave in Lead IV in Normal Children and Children with Rheumatic Heart Disease, ibid. **12**:88-104 (July) 1936. (*h*) Rosenblum, H., and Sampson, J. J.: A Study of Lead IV of the Electrocardiogram in Children with Especial Reference to the Direction of Excursion of the T Wave, ibid. **11**:49-52 (Jan.) 1936. (*i*) Burnett, C. T., and Taylor, E. L.: Electrocardiograms of One Hundred and Sixty-Seven Average Healthy Infants and Children, ibid. **11**:185-205 (April) 1936. (*j*) Messeloff, C. R., and Pomerantz, A.: A Study of Lead IV in Normal Children and Ambulatory Children with Cardiac Disease, Am. J. Dis. Child. **53**:1485-1489 (June) 1937. (*k*) Hafkesbring, E. M.; Drawe, C. E., and Ashman, R.: Children's Electrocardiograms: I. Measurements for One Hundred Normal Children, ibid. **53**:1457-1469 (June) 1937. (*l*) Ashman, R., and Hull, E.: Essentials of Electrocardiography, New York, The Macmillan Company, 1937.

3. Levy, R. L., and Turner, K. B.: Impaired Auriculo-Ventricular Conduction in Rheumatic Fever, Arch. Int. Med. **43**:267-273 (Feb.) 1929. Lichty, J. M.: The Value of the Electrocardiogram in the Study of Children's Hearts, Pennsylvania M. J. **32**:751-754 (Aug.) 1929. Brakely, E.: The Electrocardiogram in Children with Milder Degrees of Chronic Rheumatic Heart Disease, Arch. Pediat. **51**:749-757 (Dec.) 1934. Levy, R. L., and Bruenn, H. G.: Lead IV of the Electrocardiogram in Rheumatic Fever, Proc. Soc. Exper. Biol. & Med. **32**:559-561 (Dec.) 1934. Footnotes 1 and 2.

A total of 118 electrocardiograms were made in the usual manner on the Hindle instrument.[4] In addition to the three standard leads precordial leads were taken in 44 instances. Serial studies were done on 25 patients. Changes due to digitalis, which were present in only a few electrocardiograms, were disregarded. No other drug which might have produced alterations had been given.

CRITERIA FOR DETERMINATION OF ELECTROCARDIOGRAPHIC ABNORMALITY

The following standards for abnormality in the electrocardiograms were used:

P wave: A height of 3 mm. or more in any lead, but particularly in lead II; a width of 0.1 second or more, particularly if associated with notching; conspicuous notching in lead I or lead II.

PR interval: A width of 0.19 second or more.

QRS complex: Conspicuous notching in lead I or leads I and II; significant slurring in two or more leads, unaccompanied by low voltage; low voltage (maximum amplitude 5 mm.) in all leads.

RS-T segment: Deviation (elevation or depression) of the RS-T segment of 1 mm. or more above or below the isoelectric line; absence of isoelectric ST interval, particularly in lead I or lead II or both.

T wave: Low, flat, diphasic or inverted T wave in lead I or in leads I and II.

QT interval: See the table given by Ashman and Hull.[21]

Axis deviation: Angles of axis deviation greater than 90 degrees or less than 30 degrees except for slight right axis deviation in infants and deviation explained by body habitus.

Rhythm: Any disturbance of rhythm, exclusive of sinus arrhythmia, sinus tachycardia and sinus bradycardia.

Lead IV [5]*:* Tall broad P wave; absence of Q wave; deviation of ST interval of more than 2 mm. below or of any extent above the isoelectric line; prolonged span of QRS complex; conspicuous notching or triphasic contour of QRS complex; T waves above 9 mm. in amplitude.

Serial Records: Any conspicuous change from record to record, particularly in leads I and II. Changes in QRS-T_3 and T_4 were interpreted with caution because of their variability in normal single electrocardiograms as well as in serial records.

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4. Made by the Cambridge Instrument Co., Inc., New York.

5. This term as used is based on the previous method of leading in which lead IV represents a precordium to left leg lead, taken over lead II, with the right arm lead wire attached to the precordial electrode.

RESULTS AND COMMENT

Table 2 illustrates the distribution of the individual alterations in waves in the entire series of 118 electrocardiograms. The results are divided arbitrarily into five groups on the basis of the cardiac involvement demonstrable by clinical means. Of the 70 patients, 49, or 70 per cent, had one or more electrocardiographic abnormalities. The specific changes in the contour of individual waves were in accord with those previously described. Deformities of the P waves consisted largely of increased height, width and notching and occurred only in the records of the patients of groups 1 and 2, that is, those with the most extensive cardiac involvement. Heart block was present in only 6 instances; dropped beats occurred in none, and the maximum PR interval recorded was 0.26 second. The QRS abnormalities were confined principally to notching and slurring. Low voltage was encountered in only 3 instances and intraventricular block was not observed. The changes in the RS-T segment were those observed by Cohn and Swift [1a] and by Rothschild, Sachs and Libman.[1e] Alterations of the T waves consisted of rounding, flattening, diphasic contour and inversion. The fact that all disturbances of the RS-T segments and of the T waves were present only in the records of the patients in groups 1, 2 and 3, in whom myocardial injury was greatest, probably indicates the diagnostic significance of these abnormalities. The QT interval, prolonged in 17 instances, was singly abnormal in only 3. The angles of axis deviation varied from + 117 to — 147 degrees, with right axis deviation slightly predominant.

Of 51 patients for whom a diagnosis of mitral insufficiency or mitral stenosis was made, 7 had changes in the P wave and 13 had axis deviation (8 to the right and 5 to the left). There is thus little correlation between the alterations of the mitral valve and the changes in the electrocardiogram. The rhythmic disturbances consisted of sinoauricular block, shifting pacemaker, nodal rhythm and premature beats, both auricular and ventricular, with no instances of auricular fibrillation or of auricular flutter. Lead IV, taken for 44 patients, was abnormal for 14, principally patients in groups 1 and 2, but it was of little value since it was the single abnormality in only 1 instance. The changes observed in serial records were notching and widening of the P waves; increase or decrease in the PR interval; slurring, notching and changing voltage of the QRS complex; shifting of the electrical axis; elevation, depression or return of the isoelectric RS-T interval; variations in the amplitude and direction of the T wave, and changes in the cardiac rhythm. For only 3 patients were serial records (2 each) uninformative, which clearly illustrates the importance of such records.

While there may be no close or specific correlation of the electrocardiographic changes with the clinical observations, as was pointed out

TABLE 2.—*Distribution of Individual Alterations in Waves in Electrocardiograms of Seventy Patients with Rheumatic Fever and Rheumatic Carditis*

	No. of Patients	No. of Electrocardiograms	No. of Patients with Serial Electrocardiograms	P Wave	PR Interval	QRS Complex	RST Segment	T Wave	QT Interval	Axis Deviation		Changes in Rhythm	Lead IV	Serial Changes	No. of Patients with Abnormalities	Percentage of Patients with Abnormalities
										Right	Left					
1. Rheumatic carditis of fatal termination	9	14	4	3	2	4	1	5	1	3	1	0	6	Notching of P wave; shifting of axis; decrease in PR interval; in amplitude of T wave	9	100
2. Rheumatic carditis with congestive failure	13	31	6	6	1	8	4	5	2	4	0	0	5	Voltage increased; shifting of axis; notching and widening of P wave; changes in RST segment and T wave; notching of QRS_4; appearance of Q_4	13	100
3. Rheumatic carditis with cardiac enlargement	24	38	7	0	1	9	2	2	9	3	3	2	1	Voltage; axis deviation; changes in P wave; prolongation of PR; notching and slurring of QRS; changes in RT segment and T wave; shifting rhythm	16	67
4. Rheumatic carditis with no cardiac enlargement, murmurs only	15	23	6	0	2	4	0	0	4	0	4	2	1	Axis deviation; decrease in PR interval; notching, splintering and shifting voltage of QRS; changes in T wave	8	53
5. Rheumatic fever with no clinical cardiac involvement	9	12	2	0	0	1	0	0	1	2	0	0	1	Changes in T wave	3	33
	—	—	—	—	—	—	—	—	—	—	—	—	—		—	—
Totals	70	118	25	9	6	26	7	12	17	12	8	4	14		49	70

by Reid and Kenway [1f] and Shapiro,[1h] the electrocardiograms of the 22 patients who had the most extensive myocardial damage (groups 1 and 2) were all abnormal. Of the 48 patients in the other three groups alterations were present in the electrocardiograms of 66 per cent of the 24 in group 3 and of 53 per cent of the 15 in group 4, patients in whom the cardiac involvement was slight to moderate, and of only 33 per cent of the 9 in group 5, patients in whom heart disease could not be demonstrated clinically. Fewer serial records were obtained for patients in group 5 because most of these patients were ambulatory and infrequently observed.

CONCLUSIONS

The results of a study of 118 electrocardiograms of 70 children who had rheumatic fever and varying degrees of cardiac damage are reported.

The electrocardiograms of 49, or 70 per cent, of the 70 patients, disclosed one or more abnormalities in single or serial tracings.

The electrocardiograms of the patients who had the greatest degree of myocardial injury were most frequently abnormal.

Satisfactory criteria of electrocardiographic abnormality in single or serial records are listed.

DEVELOPMENTAL PATTERN OF THE CHILD AS REFLECTED IN THE CALCIFICATION PATTERN OF THE TEETH

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AND

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The purpose of this investigation was to study the effect of the different stages in the development of the child on the quality and the degree of calcification of the enamel and the dentin and to describe the characteristics of the developmental periods as revealed by the changes recorded within these structures.

GENERAL CONSIDERATIONS

Mode of Tooth Growth.—The hard tissues of the teeth, the enamel and the dentin, grow by the formation of a layer of new substance on the old (fig. 1). Such activity is termed appositional, or additive, growth, as distinguished from proliferative, or multiplicative, growth. The former is the result of cellular secretion; the latter is the result of cellular division.

The appositional type of growth results in the formation of concentric layers, or rings, and is well illustrated in the trunk of the tree. The cambium, under the bark, is analogous to the formative layers in the tooth (the amelogenic layer of the enamel organ and the dentinogenic layers of the pulp). The hard tissues of the teeth thus form by the deposition of a new layer on the old, the enamel from within outward and the dentin from without inward (fig. 2).

The formation of these layers is characterized by the regular and rhythmic manner in which it proceeds, in accordance with definite laws of growth, which have been analyzed by Schour and Massler.[1]

This investigation was aided by grants from the Carnegie Corporation of New York and Mead Johnson & Co.

From the Department of Histology, University of Illinois College of Dentistry, and the Department of Pediatrics, University of Illinois College of Medicine.

1. Schour, I., and Massler, M.: Studies in Tooth Development: The Growth Pattern of Human Teeth, J. Am. Dent. A. **27**:1778 (Nov.); 1918 (Dec.) 1940.

Each deposition is termed an incremental ring, or layer. Since the deposition of these layers is regular, their chronologic sequence can easily be determined. This fact has been successfully applied in tree ring analysis.[2] The pattern of appositional growth in the teeth as indicated by the exact chronologic sequence of the incremental rings, or layers, has been fully described in a recent report.[1] This pattern is utilized in this study (fig. 6).

Sensitivity of Growing and Calcifying Tissues to Metabolic Variations.—The layers of enamel and dentin are extremely sensitive to variations in metabolic processes during their formation and calcification.

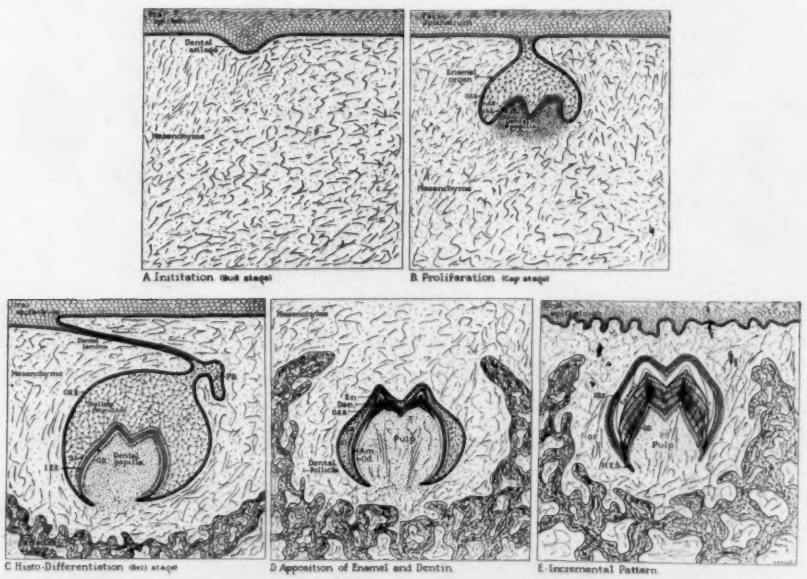
A Initiation (bud stage)
B Proliferation (cap stage)
C Histo-Differentiation (bell stage)
D Apposition of Enamel and Dentin
E Incremental Pattern

Fig. 1.—The mode of formation of the enamel and the dentin of the lower deciduous molar. *Am.* signifies ameloblasts; *Den.*, dentin; *D.F.*, dental follicle; *En.*, enamel; *H.E.S.*, Hertwig's epithelial root sheath; *I.E.E.*, inner enamel epithelium; *Od.*, odontoblasts; *O.E.E.*, outer enamel epithelium; *P.B.*, permanent tooth bud; *R.E.E.*, reduced enamel epithelium; *S.I.*, stratum intermedium, and *S.R.*, stellate reticulum.

Alterations in the internal environment of the body are therefore recorded in the incremental layers, or rings, developing at the time. This is similar to the effects of seasonal changes, drought and temperature on the growth of the tree. Environmental variations affect the

2. Douglass, A. E.: Tree Growth and Climatic Cycles, Scient. Monthly **37**: 481-495, 1933.

layer or ring forming at the time they occur, and the resulting characteristic formation of that layer thereafter constitutes a permanent record of the fluctuations.

However, once a given layer of enamel and dentin is fully formed and calcified, it cannot be altered structurally by systemic factors. This

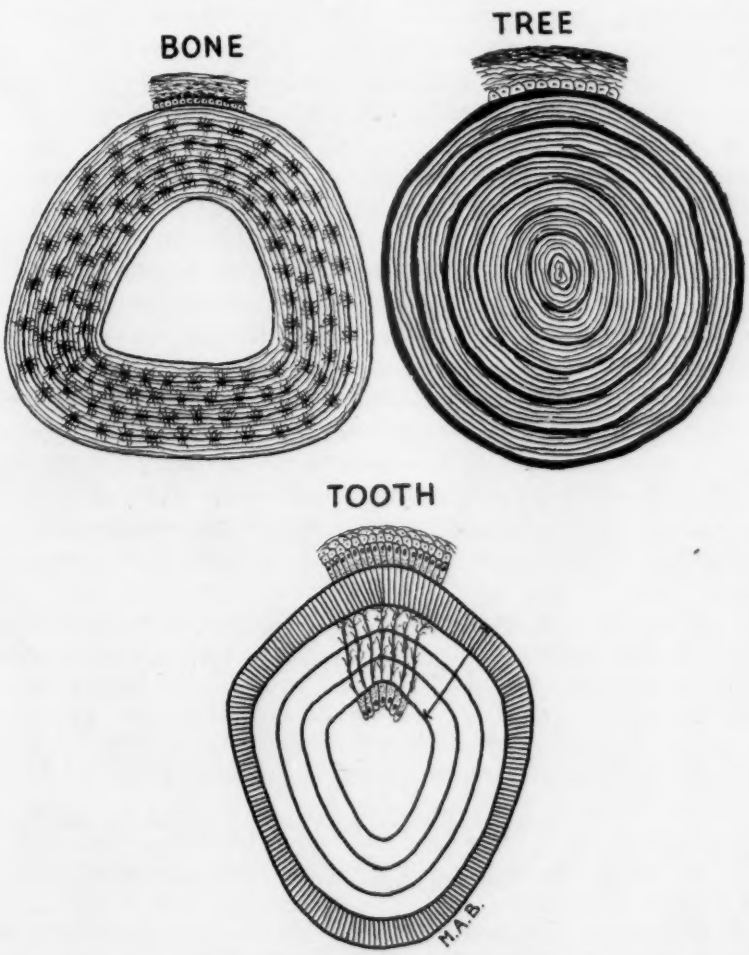

Fig. 2.—The mode of ring formation in bone, tree and tooth. Part of the formative organs are indicated. Note that the formation of bone, tree and enamel is from within outward but that the formation of dentin is from without inward.

is because the formative cells have receded and lost their connection with the matrix itself. In the dentin the encapsulated dentinal fibrils, protoplasmic processes from the odontoblasts in the pulp, give "vitality" to that tissue, but the matrix itself is nonvital. For this reason the

records produced by systemic variations remain permanent and unaltered in the layers of the enamel and dentin, as do the analogous records of environmental changes in the rings of the tree. Only external factors can erase such records in the teeth (caries, erosions and abrasions) or in the tree (fire).

Bone also grows and calcifies in an appositional manner. It also records within its structure, in the form of accentuated transverse, or "arrest," lines, the effects of disturbances in body metabolism (Eliot, Souther and Park [3]). However, the records in bone are erased by the constant resorption and reconstruction which occur in this more plastic tissue.

Recording Quality of the Enamel and Dentin.—Thus, the enamel and dentin in the formative and calcifying stages of their growth serve as kymographs on which are permanently recorded the physiologic or pathologic changes in metabolism that occur within the organism. This concept has been verified many times by histologic studies of the teeth of experimental animals and of man (Schour [4]).

Tooth Ring Analysis.—The different stages in the development of man are well known (Bean [5] and Robertson [6]), and their characteristics have often been described. It is also recognized that each developmental stage produces characteristic differences in the development of the teeth (Mellanby [7] and Swanson [8]); so the characteristic modification in the calcification of the enamel and the dentin formed during a given chronologic period mirrors the constitutional status of the subject during that period.

The analysis of the effects of systemic variations on the growth and the calcification of the enamel and the dentin has been termed tooth ring analysis (Schour [4]).

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3. Eliot, M. M.; Souther, S. P., and Park, E. A.: Transverse Lines in X-Ray Plates of the Long Bones of Children, Bull. Johns Hopkins Hosp. **41**:364-388 (Dec.) 1927.

4. Schour, I.: Calcium Metabolism and Teeth, J. A. M. A. **110**:870-877 (March 19) 1938.

5. Bean, R. B.: The Pulse of Growth in Man, Anat. Rec. **28**:45-61 (June) 1924.

6. Robertson, T. B.: Studies on Growth of Man: I. The Prenatal and Postnatal Growth of Infants, Am. J. Physiol. **37**:1-42 (April) 1915.

7. (*a*) Mellanby, M.: The Structure of Human Teeth, Brit. Dent. J. **48**:737-751 (July) 1927; (*b*) Diet and the Teeth: An Experimental Study, Medical Research Council, Special Report Series, no. 191, London, His Majesty's Stationery Office, 1934.

8. Swanson, J. H.: (*a*) Age-Incidence of Lines of Retzius in the Enamel of Human Permanent Teeth, J. Am. Dent. A. **18**:819-826 (May) 1931; (*b*) The Relation of Growth Velocity to the Quality of the Enamel, ibid. **18**:2174-2176 (Nov.) 1931.

REVIEW OF LITERATURE

A review of the literature shows that comparatively few studies have been made to determine accurately the quality of tooth structure during different age periods, or even to determine the effects of systemic factors on the quality of the tooth structure. The work of Mellanby,[7] Swanson,[8] Karnosh [9] and Schour [10] represent the major endeavors in this direction. Mellanby [7] and Schour [10] investigated the quality of the enamel and the dentin formed during different age periods in deciduous and in permanent teeth. They judged the quality of the enamel by the number of incremental lines (bands of Retzius) per unit area; the more lines there were, the poorer was the quality of the enamel. Mellanby [7] used the number and the size of the interglobular spaces in the dentin as the index for classifying the quality of the tooth structure. This is similar to the method used in this laboratory.

Most investigators agree that the tissue formed before birth is better calcified than that formed after birth. Mellanby [7a] and Swanson [8a] found that age periods favorable or inimical to the calcification of the dental tissues might be listed as follows (table 1): (1) inception of calcification to about 6 months in utero—good calcification; (2) 6 months in utero to 6 months of age—poor calcification; (3) 6 months to approximately 2 years of age—good calcification; (4) the third, fourth and fifth years of life—poor calcification; (5) from the end of the fifth year to about 10 years of age—good calcification, and (6) prepuberty and puberty—poor calcification. Their observations on the levels of the teeth which show good and poor calcification agree for the most part with ours, but their demarcation of the age periods differs somewhat from ours. These differences are due to the fact that the chronologic tables of tooth formation used by these authors were inaccurate, the dating of the incremental lines being virtually unknown, and that such biologic landmarks in the teeth as the neonatal ring [10] had not yet been discovered. Table 1 summarizes their observations and gives a corrected chronology on the basis of more recent knowledge about the growth of the teeth.

Swanson [8b] correlated the periods of good and poor calcification with the slow and rapid rates of body growth as indicated by Robertson. The correlations of slow body growth with good calcification of the dental tissues and rapid body growth with poor calcification are, however, only approximate.

Swanson [8a] also mentioned the presence of accentuated incremental lines in the enamel of the incisors and first permanent molars at about

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9. Karnosh, L. J.: Histopathology of Syphilitic Hypoplasia of Teeth, Arch. Dermat. & Syph. **13**:25-42 (Jan.) 1926.

10. Schour, I.: The Neonatal Line in the Enamel and Dentin of the Human Deciduous Teeth and First Permanent Molar, J. Am. Dent. A. **23**:1946-1955 (Oct.) 1936; footnote 4.

TABLE 1.—*Comparative Data for Periods of Good and Poor Calcification of Deciduous and Permanent Teeth* *

Teeth †	Levels Examined	Quality of Calcification of Enamel: Mellanby [7] and Swanson [8]	Quality of Calcification of Enamel: Massler, Schour and Poncher	Age Period According to Mellanby and Swanson	Corrected Age Period
I II III / a b c; IV V / d e	Incisal ⅔; Cuspal ⅓	Good	Excellent	Inception of calcification to about 6 months in utero	4 months in utero to birth
I II III / a b c; IV V / d e	Cervical ⅓; Middle and cervical ⅔	Poor	Very poor	6 months in utero to 4 to 6 months after birth	Birth to about 10 months of age
6 / 6	Occlusal ⅓				
6 / 6; 1 3 / 1 2 3; 2; 4 5 7 / 4 5 7	Middle ⅔; Narrow band between incisal and middle ⅓ ‡; Incisal ⅓; Cuspal area	Good	Good	4 to 6 months to about 2 years of age	10 months to about 2½ years of age
6 / 6; 1 2 3 / 1 2 3; 4 5 7 / 4 5 7	Cervical ⅓; Cervical ½; Middle ⅔	Poor	Poor	3 to 5 years of age	About 2½ to 5 years of age
3 7 / 3 7; 8 / 8	Cervical ⅓; Occlusal ½	Good	Fair	6 to 10 years of age	6 to 10 years of age
8 / 8	Cervical ⅓	Poor	Poor	About 10 to 13 years of age	About 10 to 13 years of age

* Note that the age periods for the formation of the levels appearing before the first year are the only essential differences in the results of the three investigators.

† In the dental formula permanent teeth are indicated by Arabic numerals, maxillary deciduous teeth by Roman numerals and mandibular deciduous teeth by letters.

‡ Both Mellanby and Swanson included in this period the development of the cuspal enamel of the anterior teeth, and they therefore begin this period at 4 to 6 months of age. The development of this area, which appears well calcified, has, however, like mantle dentin, no chronologic significance, and we therefore omit it. We begin this period at 10 months of age, on the basis of observations on the upper lateral incisor, which begins to form at about that time.

1 year of age, which he attributed to weaning, and four regularly spaced wide lines in the anterior teeth, which he suggested might be due to the reduction in sunlight during the winter months.

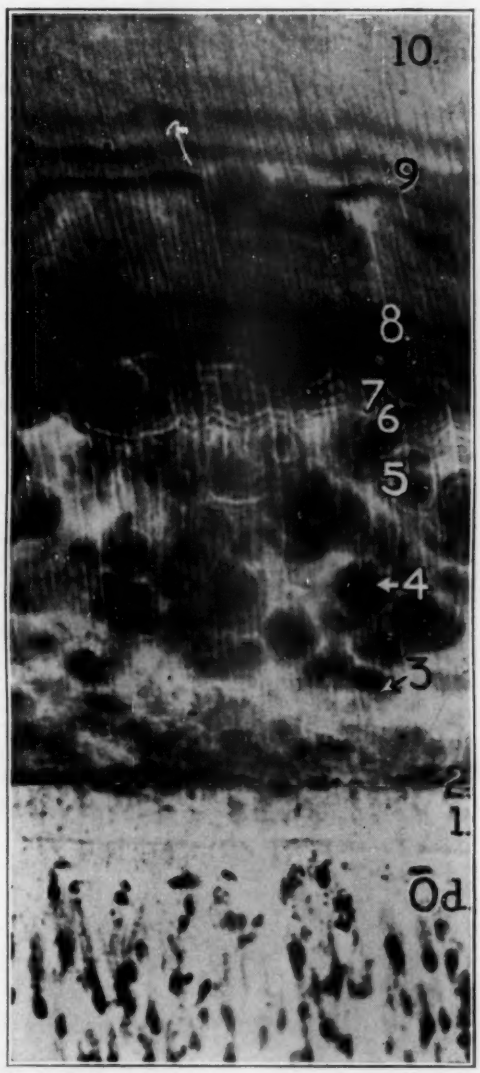


Fig. 3.—Photomicrograph showing the steps in the calcification of the dentin. This section was taken from the tooth of a rat fed a rachitogenic diet. As the rat became more rachitic the calcification of the dentin became more incomplete, until all stages from the most perfect to the least perfect calcification were depicted. Compare with figure 5*A*, which is a diagrammatic representation of this figure. The numbers in this figure correspond to those in figure 5*A*.

The data of each investigator pertinent to the subject will be discussed under the different age periods.

FORMATION AND CALCIFICATION OF HARD TISSUES

In the consideration of hard tissues it is important to distinguish between the formation, or deposition, of the matrix and its subsequent calcification, or mineralization. The matrix is produced as an extracellular product, and calcification occurs by the precipitation of inorganic calcium salts within the deposited matrix.

Calcification begins within the deposited matrix by the precipitation of a small nidus, about which further precipitations occur, so that the original nidus increases in size by the addition of concentric laminations (figs. 3 and 4). Such a formation of precipitates is termed a calcospherite. In a given layer of bone or tooth matrix the formation of many such calcospherites results in the eventual approximation and consequent fusion of the individual calcospherites into a homogeneously or smoothly mineralized layer of tissue matrix. When calcification is disturbed or deficient the individual calcospherites in the dentin do not fuse and remain as discrete isolated basophilic calcospherites in a field of uncalcified eosinophilic matrix (fig. 5). Such deficiencies are most readily recognized in the dentin (and are called interglobular dentin), but they can also be recognized, although not so clearly, in calcifying enamel or bone.

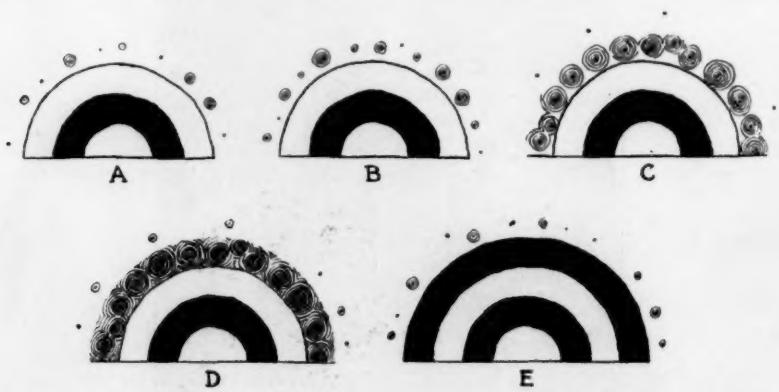


Fig. 4.—Concrement formation in vitro (modified after Schade, in Alexander, J.: Colloid Chemistry, New York, Chemical Catalog Company, Inc., 1928, vol. 2, chap. 46, p. 829). Note the formation of calcospherites and the *Liesegang* ring phenomenon.

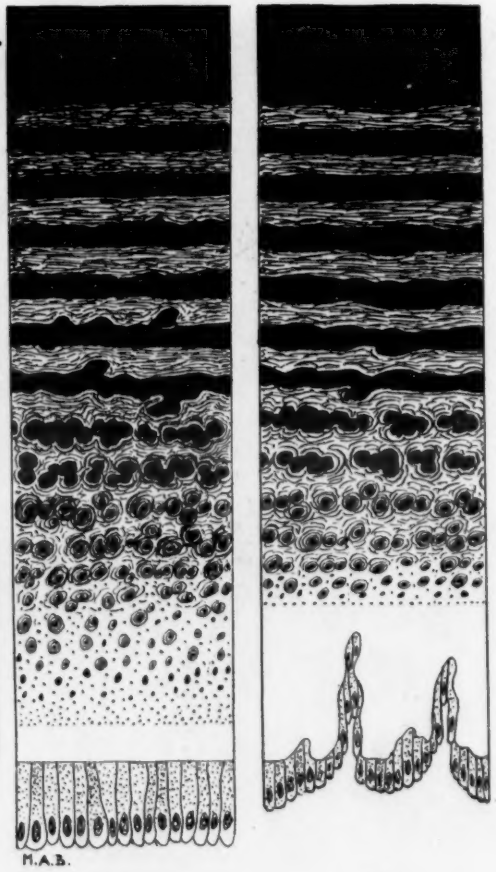
The formation and calcification of the matrix of the teeth and bones are not smooth, unvarying processes but occur in a rhythmic alternation that is perhaps related to a physiologic diurnal rhythmicity in cellular

Stages in the Calcification of Dentin

10. Very well calcified layer at dentin surface (mantle dentin)
9. Rhythmic alternation of stratification
8. Fusion of calcospherites into a homogeneous incremental layer
7. Fusion of calcospherites practically complete (dappled or areolar dentin)
6. Incomplete fusion of calcospherites
5. Approximation and beginning of fusion of calcospherites
4. Increase by concentric laminations
3. Isolated calcospherites
2. Beginning of calcification (intermediate dentin)
1. Uncalcified predentin

Interglobular dentin

Odontoblasts



Response of Developing Dentin to Systemic Disturbances

Perfect calcification

Mild systemic effect

Physiologic
- Accentuation of incremental stratification
- Dappled dentin (Beust)

Subclinical
- Areolar dentin (Mellanby)

Pathologic (Interglobular dentin)
- Incomplete fusion of calcospherites
- Incomplete separation of calcospherites
- Complete separation of calcospherites
- Completely isolated calcospherites
- Wide predentin
- Pathologic degeneration of odontoblasts with pulpal inclusions (dentin hypoplasia)

Severe systemic effect

activity and mineral metabolism. As a result the calcified tissues normally show a stratification that represents the so-called incremental growth lines, which are called bands of Retzius in the enamel, Owen's lines of contour in the dentin and cementing lines in bone. In a sense they may be compared with the growth rings in the tree. The stratifications in the dentin of most species tend to recur in increments of 16 microns (Schour and Hoffman [11]).

METHOD OF EVALUATING THE QUALITY AND DEGREE OF CALCIFICATION OF TEETH

All sections were examined under transmitted light. The density of the calcification was judged by the degree of translucency and the homogeneity of the structure.

Enamel.—The appearance of the enamel under transmitted light was used as an index of its calcification. Thus the density of the calcification was judged by its degree of translucency and whiteness. Areas that appeared dark or black were regarded as poorly calcified. The number of incremental lines was used as another index of calcification, the greater their number, the lesser the degree of calcification. Swanson [8a] recognized that the striae of Retzius "range in a graded series from scarcely perceptible striations to relatively grave lesions, and reflect, by their magnitude and number, the changes that took place in the salt balance of the body as enamelization proceeded."

Hypoplasia of the Enamel.—If a systemic disturbance is sufficiently severe, not only the calcification of the matrix but the cells active at the time in the deposition of the matrix will be affected. The result may be a lack of matrix formation. This occurs usually in the enamel, the dentin being less frequently affected, and is termed hypoplasia. Hypoplasia may be considered as indicative of a severe systemic disturbance. Analysis of hypoplastic defects thus supplements the information obtained by the analysis of calcification.

The epithelial enamel-forming cells are much more sensitive to systemic interferences than are the mesenchymal dentin-forming cells. Whereas a severe systemic disturbance may be reflected in the presence of interglobular dentin in the dentin, the enamel-forming cells are often injured by the same effect and in such a manner that hypoplastic enamel results (table 2). The effect on the calcification of the enamel is therefore obliterated by the lack of formation.

Hypoplastic effects can thus be taken to indicate also severe disturbances in calcification.[12] A consideration of the incidence of enamel hypoplasia is therefore included in this study because such formations reflect periods of severe systemic imbalance or of high cellular susceptibility to systemic interferences.

Table 2 gives some criteria by which the degree of calcification of the enamel may be evaluated.

Dentin.—Although much more difficult to observe microscopically, the quality and degree of calcification of the dentin are easier to evaluate. The variations in the degree of calcification of the dentin are more extensive and therefore more

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11. Schour, I., and Hoffman, M. M.: Studies in Tooth Development: I. The Sixteen Microns Calcification Rhythm in the Enamel and Dentin from Fish to Man, J. Dent. Research **18**:91-102 (Feb.) 1939.

12. Schour, I.: Tooth Development, in Gordon, S. M.: Dental Science and Dental Art, Philadelphia, Lea & Febiger, 1938.

easily and objectively graded (fig. 5 *B*). While the enamel is more sensitive than is the dentin to minor fluctuations in calcium metabolism, its range of reaction is more limited. The dentin can respond to such fluctuations in a greater variety of ways and therefore depicts the different degrees of fluctuation more accurately.

The severity of a given systemic interference is reflected in the quality of the calcification—the more severe the disturbance the more incomplete the process of calcification (fig. 3). Figure 5 *B* is a diagrammatic representation of the response of calcifying dentin to systemic interferences, and data for evaluating the response are given in table 2. The basis for evaluation of the degree of calcification in the dentin may be summarized as follows:

1. A smooth, homogeneous calcification showing no incremental lines is considered good.

TABLE 2.—*Response of Developing Dentin and Enamel to Systemic Disturbances*

Systemic Effect	Reaction in Dentin	Reaction in Enamel
Mild		
Physiologic		Accentuation of incremental lines (bands of Retzius)
	Accentuation of incremental stratification (Owen's lines of contour)	
		Increased no. of striae and pigmentation
	Dappled dentin (Beust)	
Subclinical	Areolar dentin (Mellanby)	
		Hypocalcification (mottled, chalky enamel)
	Incomplete fusion of calcospherites	
Pathologic	Interglobular dentin	
	Isolated calcospherites Wide predentin	(Ameloblasts show pathologic degeneration)
		Lines of arrested or deviated growth
	(Odontoblasts show pathologic degeneration) Lines of arrested or deviated growth	Hypoplastic defects
	Hypoplastic defects (pulpal inclusions)	
Severe		

2. The appearance of the normal incremental stratification is considered to be within the normal physiologic variations of the process of calcification.

3. The imperfect fusion of the calcospherites, which gives a granular appearance to the dentin (dappled dentin of Beust and areolar dentin of Mellanby), is considered to indicate a subclinical deficiency in calcification. The presence of interglobular dentin, or the incomplete fusion of the calcospherites, is considered to be an indication of a marked disturbance in calcification. This interglobularity is subdivided into four degrees, which indicate the severity of the disturbance in calcification (figs. 3 and 5): (*a*) incomplete fusion of the calcospherites, which gives to the dentin a distinctly mottled appearance; (*b*) complete separation of the calcospherites; (*c*) complete isolation of the individual basophilic calcospherites in a field of acidophilic, eosin-staining, uncalcified dentin matrix, and (*d*) usually associated with this, a wide predentin border of uncalcified dentin.

4. Prominent and acute accentuation of any one or several incremental lines is considered to indicate an acute disturbance in calcification and generally an arrest in matrix formation rather than a primary effect on calcification (fig. 12).

5. Death of the dentin-forming cells in localized areas results in the formation of pulpal inclusions, or hypoplastic defects. These are rarely seen and occur only in cases of the most severe systemic disturbances, such as prolonged parathyroprivic tetany.

MATERIAL

The laboratory of histology of the University of Illinois College of Dentistry has for some time received teeth, deciduous and permanent, from various parts of the country. The bulk of the material was obtained from several sources in Chicago: dental clinics, private practitioners and parents, who cooperated by saving all the shed or extracted teeth of their patients or children. Most of the teeth were accompanied by medical histories of the patients.

This study is based on about 1,000 human deciduous and permanent teeth from normal, healthy children, which were studied in ground and decalcified sections. The teeth were distributed evenly among the deciduous and permanent dentitions, and incisors, cuspids and molars were fairly evenly represented. The decalcified sections were usually stained with hematoxylin and eosin.

The data on the incidence of hypoplastic defects herein recorded were those obtained from observing patients regularly admitted to the dental clinics of the University of Illinois. These patients were examined for dental caries, and hypoplastic defects were noted at the same time.

A study of the effects of various dietary and endocrine disturbances on the quality of the dental tissues is being made, and the results will be presented in a subsequent report.

RESULTS

Prenatal Calcification.—Calcification begins in the deciduous teeth at the age of 4 to 6 months in utero. The incisal four fifths and the occlusal one third of the crowns of all the deciduous teeth were therefore examined (figs. 6, 7 and 8). In some instances the first permanent molars showed a small amount of prenatal calcification immediately over the mesiobuccal growth center or dentin cusp.

Enamel: The enamel formed before birth is characteristically white and translucent. The calcification appears to be homogeneous and dense, relatively few incremental bands being present.

Dentin: The dentin is also homogeneously and densely calcified. Few incremental lines can be observed, and these are usually of a distinctly normal appearance. Less than 10 per cent of the teeth showed a slight increase in the prominence of the normal incremental stratification. In only 2 cases was any abnormal disturbance in prenatal calcification observed.

Hypoplastic Defects: Hypoplastic defects in tissue calcified before birth were not found in our histologic material, but 3 patients with such defects were observed in the children's clinic at the University of Illinois.

Neonatal Ring.—The deciduous teeth and the mesiobuccal cusp of the first permanent molars regularly show an accentuated incremental ring at the level of the enamel and the dentin which is forming and calcifying at about the time of birth (figs. 6 and 9 *A*). The presence of

the ring can be demonstrated in virtually all deciduous teeth if sections are carefully prepared in a sagittal plane. It is much more readily apparent in the enamel than in the dentin. It appears dark or hypocalcified in the enamel and light in the dentin. This ring probably represents a line of arrested growth rather than a line of disturbed calcification and may be compared with the arrest lines described by Eliot and his co-workers [8] and by Harris.[13]

Hypoplastic Defects: Hypoplastic defects in the neonatal ring were found in only a few cases. These were analyzed and reported by Schour and Kronfeld [14] (fig. 9 *B*).

Calcification During Infancy.—Infancy is designated as the period extending from the end of the neonatal period to about the tenth month of age. We use the tenth month of age rather than the end of the first year as the termination of this period for reasons which will appear later. The levels of the enamel and the dentin of the deciduous and the permanent teeth forming during this period are shown in figures 6, 7 and 8. Note that the upper lateral incisor, the bicuspids and the second and third molars have not yet begun their formation. The lag in the beginning of formation of the upper lateral incisor was pointed out by Zsigmondy [15] in 1894. It begins its formation at about the tenth month, at the end of the infancy period, and is therefore a valuable diagnostic point for the estimation of the period at which hypoplastic defects were formed.

The calcification of the dental tissues during the postnatal period is definitely less homogeneous than during the prenatal period. Accentuation of the incremental stratification in both the enamel and the dentin is the rule rather than the exception. This is most strikingly seen in the deciduous teeth, in which the calcification during the two periods (prenatal and postnatal) can be compared in the same section (fig. 9 *C*).

The decrease in the quality of the postnatal calcification becomes more marked as the age increases. Thus, the decrease in the quality of the calcification is only slight during the first three months but becomes increasingly more prominent from the third to the tenth month. At the tenth month an abrupt recovery in the quality of the calcification frequently occurs. This is true not only of the teeth of normal children; it is accentuated in those of children suffering from disturbances during

13. Harris, H. A.: Bone Growth in Health and Disease, London, Oxford University Press, 1933.

14. Schour, I., and Kronfeld, R.: Tooth Ring Analysis: IV. Neonatal Dental Hypoplasia; Analysis of the Teeth of an Infant with Injury of the Brain at Birth, Arch. Path. **26**:471-490 (Aug.) 1938.

15. Zsigmondy, O.: Beiträge zur Kenntnis der Entstehungsursache der hypoplastischen Emaildefecte, Tr. World's Columbian Dent. Cong., Chicago **1**:48-67, 1894.

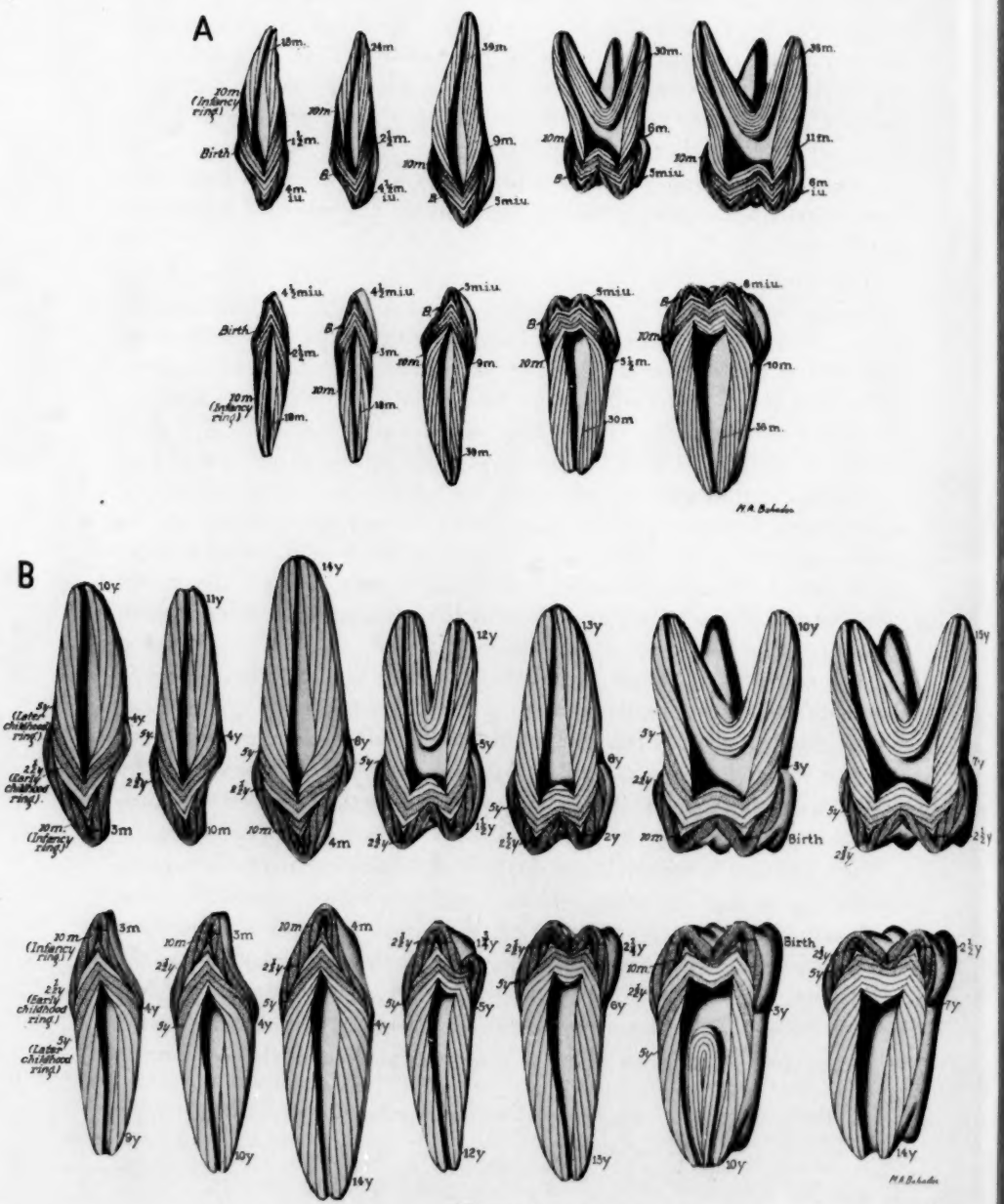

Figure 6

(See legend on opposite page)

infancy which cause marked interglobular dentin and hypoplastic defects in the enamel. A complete and sudden recovery from these defects usually occurs at the tenth month, although the illness and its clinical manifestations may persist (fig. 10 *C*).

During our analysis another fact became evident. In a group of teeth obtained from practitioners whose patients were limited to the well-to-do classes, the quality of the calcification during infancy, although poorer than that occurring in the prenatal period, was definitely better than the calcification in a second group of teeth obtained from a free extraction clinic, which served the poorer sections of Chicago. In the latter group the postnatal calcification was almost invariably poor, interglobular dentin and accentuated incremental lines in the enamel being the rule. Mellanby [7b] has observed similar differences in the calcification of teeth obtained from private sources and from dental clinics.

Hypoplasia of the Enamel: The incidence of hypoplastic defects in the enamel and marked interglobular dentin was found to be highest during this period. Over 70 per cent of the total of hypoplastic defects that occurred in our material were found to begin at birth and to extend through the infancy period. These are therefore chronic hypoplastic defects (Sarnat and Schour [16]). Usually these defects ended abruptly at 10 months of age, indicating a complete and sudden recovery from the systemic disturbance or a difference in the metabolic and cellular response of the tissues at that age, since our records generally showed no change in the clinical condition of the patient. At the age level of the tenth month, the hypoplastic defects always showed a marked accentuation.

About 1 per cent of the hypoplastic defects of the infancy period did not end at the tenth month but were so severe that they continued into the second year and beyond, affecting practically all the teeth at all levels.

16. Sarnat, B. G., and Schour, I.: Enamel Hypoplasia in Relation to Systemic Disease: A Chronologic, Morphologic and Etiologic Classification, J. Am. Dent. A., to be published.

EXPLANATION OF FIGURE 6

Fig. 6.—Diagrammatic representation of the calcification pattern superposed on the incremental pattern of human teeth and its chronology. *A* shows deciduous teeth and *B* permanent teeth in labiolingual sections. On the right of each tooth is indicated the approximate age at the beginning of tooth formation, at the completion of the crown and at the completion of the root. Each increment represents approximately three months in the development of the deciduous teeth and one year in the development of the permanent teeth. On the left of each tooth is indicated the level of the neonatal ring (birth), the infancy ring (10 months), the early childhood ring (2½ years) and the later childhood ring (5 years). The infancy (birth to 10 months) and later childhood (2½ to 5 years) periods are stippled in the dentin. In this figure *m*, signifies months; *y*, years, and *m.i.u.*, months in utero.

About 2 to 5 per cent of the hypoplastic defects of the infancy period were of the acute type and were limited to the level of the neonatal ring (hypoplasia of the neonatal ring) or the infancy ring (acute hypoplasia of the infancy ring) (table 3).

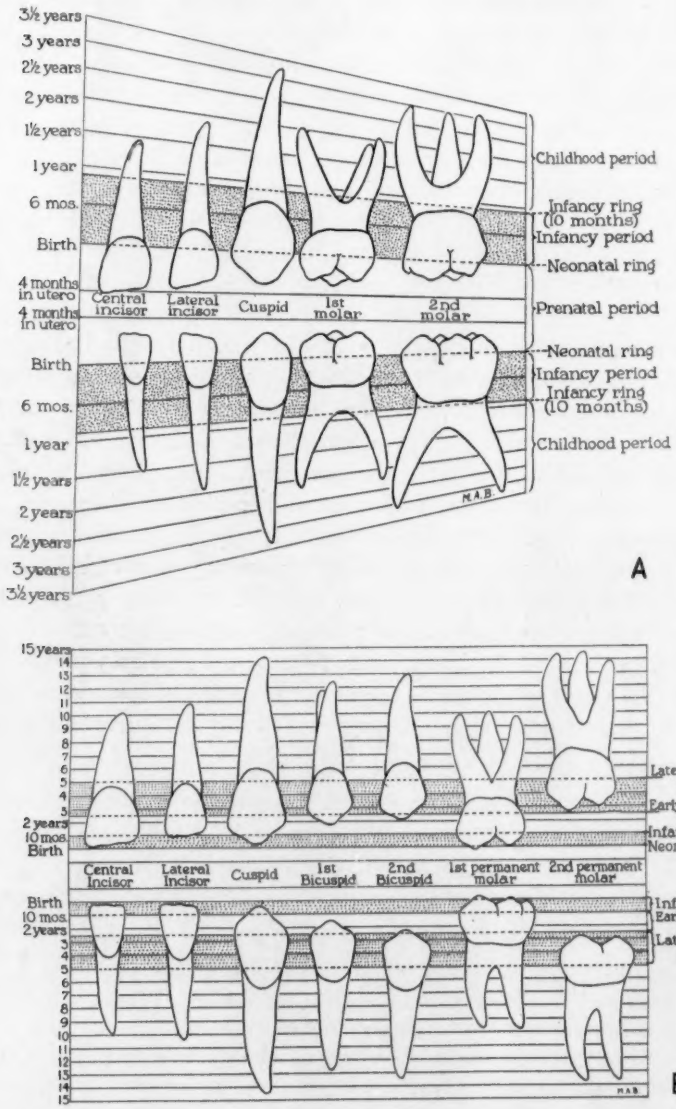

Fig. 7.—Chronology of tooth development in gross labial view, with the developmental lines and periods indicated on the right. The infancy and later childhood periods are stippled. *A*, deciduous teeth, and *B*, permanent teeth. The horizontal lines in *A* are inclined to conform with the growth gradients of the teeth (the age, locus and anteroposterior growth gradients in the dentin). The gradient in the permanent teeth is not marked and is therefore not shown.

The recognition of hypoplasia of the infancy period is facilitated by the fact that in most instances the upper lateral incisors are not involved because their formation and calcification begin at about 10 months of age (fig. 12). Thus hypoplastic defects ending at the tenth month leave the upper lateral incisors untouched. Occasionally the upper lateral incisors begin to form at about the ninth month. In such cases, the tips (*mamelons*) of the upper lateral incisors are affected by the hypoplasia of the infancy period.

Early Infancy Ring: An accentuated line can often be observed in the enamel and the dentin of the deciduous and the permanent teeth forming and calcifying at about 6 months of age. It appears more

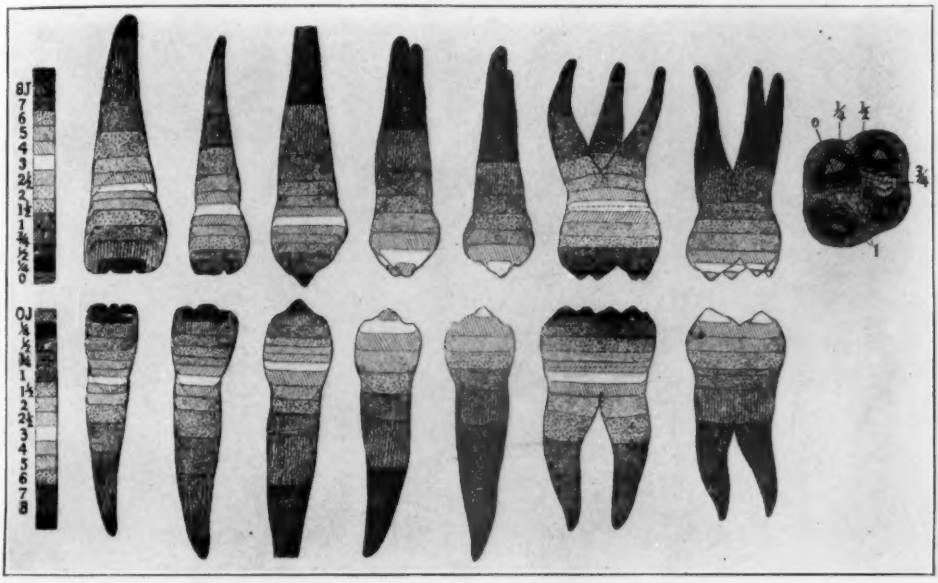

Fig. 8.—Chronology of tooth development as depicted by Berten, in 1895, on the basis of an analysis of enamel hypoplasias. This chart is more accurate than many more modern charts.

prominent in the enamel, being relatively more difficult to observe in the dentin. It appears in the enamel of 60 per cent of the deciduous second molars and permanent incisors and first molars but in the dentin of only about 25 per cent of the same teeth. Its incidence and prominence are therefore much less than those of the other rings described but are sufficiently great to warrant the tentative name of early infancy ring, since it demarcates the early infancy period from the later infancy period.

Infancy Ring: At the age of 10 months (the absolute time and the position of the ring in the teeth vary slightly) a sharply accentuated

incremental line can constantly be observed in the enamel and the dentin of both the deciduous and the permanent teeth forming and calcifying at that time (fig. 10 *A*). Because of the period at which it appears, we have termed this accentuated incremental line the infancy ring. Since the upper lateral incisor begins its formation at about the age of 10 months, the line is not visible in a gross view of this tooth but is seen only in histologic sections taken immediately over the growth center.

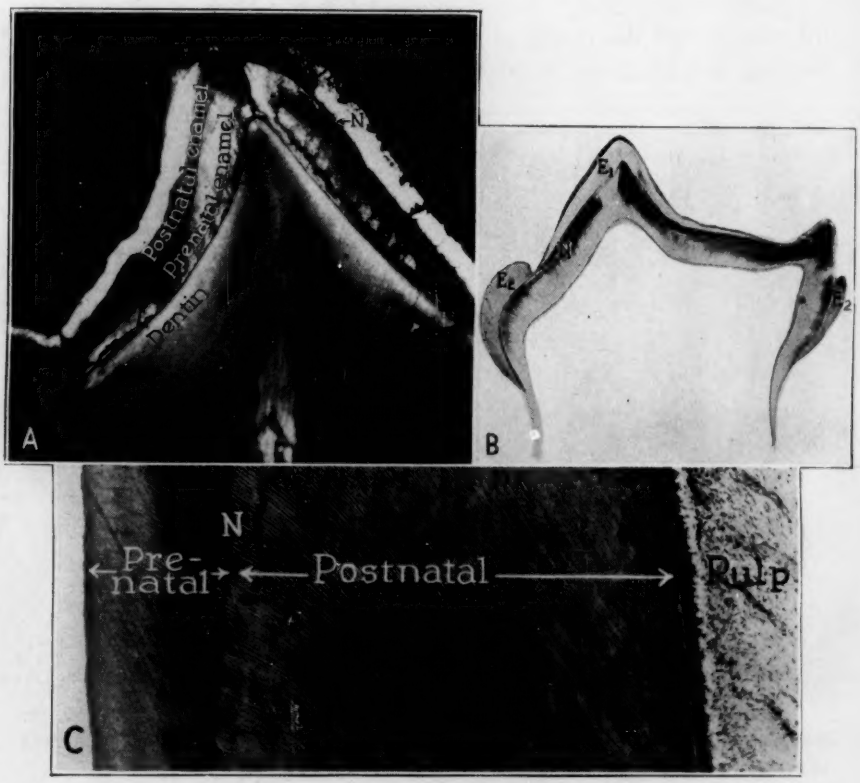

Fig. 9.—*A*, photomicrograph of a ground section of a deciduous molar taken under polarized light, showing the neonatal ring in the enamel (*N*). (This picture was supplied by Dr. H. C. Hodge.) *B*, ground section through the lower first deciduous molar of a child with birth injury and dental hypoplasia of the neonatal period. In the occlusal portion of the crown enamel formation has terminated at birth. Here only thin enamel formed before birth (E_1) is present. In the cervical portion of the crown enamel formed after birth (E_2) has made a circular ledge of normal thickness. From Schour and Kronfeld.[14] *C*, photomicrograph of the dentin of a decalcified section of a deciduous central incisor. Note that the dentin formed before birth stained deeply with hematoxylin, indicating good calcification, and that the dentin formed after birth stained less deeply with hematoxylin, indicating poorer calcification. *N* signifies the neonatal ring in the dentin.

In the deciduous teeth the line was observed only in the dentin, since formation of the enamel of these teeth had already been completed at this time (fig. 6). In these teeth it appeared in about 75 per cent of the

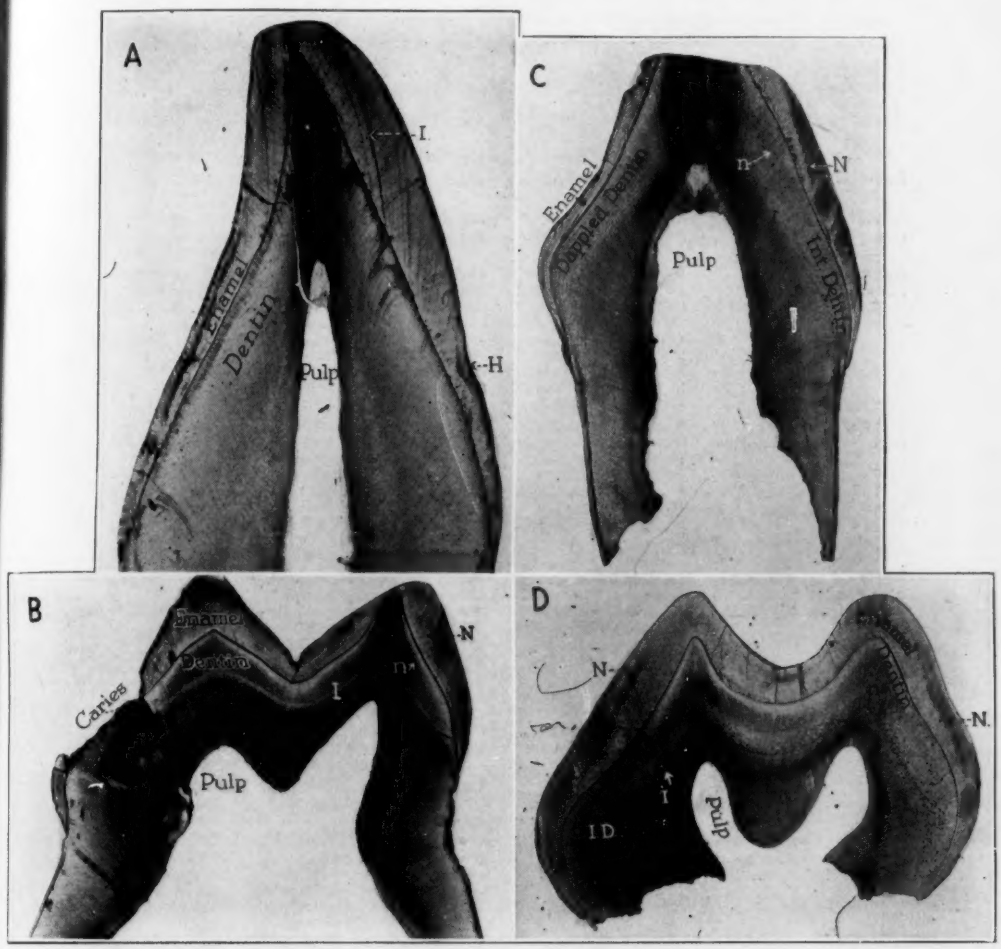

Fig. 10.—*A*, photomicrograph of a permanent lower lateral incisor, showing the infancy ring in the enamel (*I*). Note the slight hypoplastic defect (*H*) on the labial surface at about 2½ years of age (early childhood ring). *B*, photomicrograph of an upper deciduous second molar, showing marked accentuation of the infancy ring (*I*) (10 months of age) in the dentin. *N* signifies the neonatal ring in enamel; *n* the neonatal ring in dentin, and *I*, the infancy ring in the dentin. *C*, photomicrograph of a deciduous upper lateral incisor, and *D*, photomicrograph of a lower deciduous first molar, showing deficient calcification of the dentin during infancy. Note that the calcification becomes progressively less homogeneous from *n*, the neonatal ring in the dentin, to *I*, the infancy ring (10 months), and that at the level of the latter abrupt recovery occurs. *N* signifies the neonatal line in the enamel and *I D* the interglobular dentin. × 9.

sections as a hypocalcified line at the junction between two characteristic zones of calcification. In the enamel of the permanent teeth forming and calcifying at the age of 10 months (anterior teeth and first permanent

TABLE 3.—*Developmental Pattern of the Child and Its Reflection in the Teeth*

Developmental periods and Tooth Rings	Age Period	Physiologic and Developmental Characteristics	Teeth *	
			Quality of Calcification and Histologic Characteristics	Distribution of Hypoplastic Defects in the Enamel †
Prenatal	.....	Well protected parasitic existence	Good calcification	Rare
Neonatal ring	Birth to 2 weeks	Neonatal adjustments; birth trauma; arrest in growth	Dark, distinct arrest line in enamel and dentin	2% (acute hypoplasia of neonatal ring)
Infancy period	2 weeks to about 10 months	Period of postnatal adjustment; marked susceptibility to infection, disorders of alimentation and metabolic disturbances; changes in mode of growth from simple to complex	Generally poor calcification; progressively less homogeneous from third to tenth month; period of poorest calcification and greatest susceptibility to chronic hypoplastic defects; early infancy ring present at sixth month	70% (chronic hypoplasia of the infancy period)
Infancy ring	About 10 months	Time of greatest susceptibility to diseases of infancy, "critical" period; temporary depression in growth curve	Sharp arrest line in enamel and dentin demarcating infancy from early childhood period; marks a period of acute susceptibility to hypoplastic defects of the enamel as well as the abrupt termination of chronic hypoplastic defects of infancy	5% (acute hypoplasia of the infancy ring)
Early childhood period	About 10 months to 2½ years	More independent existence; improved alimentation and antibody mechanism	Recovery in calcification and cessation of hypoplasia abrupt and complete; calcification better than during infancy but not as good as during prenatal period	Relatively rare
Early childhood ring	About 2½ years	?	A sharp arrest line in enamel and dentin which demarcates early from later childhood periods; marks a period of acute susceptibility to enamel hypoplasia	5-10% (acute hypoplasia of the early childhood ring)
Later childhood period	About 2½ to 5 years	Most of the exanthematous diseases occur during this period	Calcification generally poor but better than during the infancy period	5-10% (chronic hypoplasia of the later childhood period)
Later childhood ring	About 5 years	?	A sharp arrest line in enamel and dentin which demarcates the later childhood from the grade school periods; marks a period of acute susceptibility to enamel hypoplasia	5% (acute hypoplasia of the later childhood ring)
Grade school age	About 5 to 10 years	?	Calcification generally good but variable	Relatively rare

* The levels of teeth affected are given in figures 6, 7, 8 and 12. Registration period in teeth is virtually ended after the tenth year.

† Because of the extreme sensitivity of the enamel-forming cells to metabolic disturbances, severe disturbances in calcification are manifested also as deficient enamel formation (enamel hypoplasia), which can be recognized grossly. About 5 per cent of the population suffers from these defects. The figures give the distribution of these defects according to age and type and refer to percentages of the total number of hypoplastic defects observed.

molar), the infancy ring was observed in over 90 per cent of the sections as an accentuated band of Retzius that also demarcated two zones of calcification. The corresponding line in the dentin of the permanent

teeth was much less prominent and was discernible in only about 50 per cent of the sections, although the different zones of calcification were readily apparent. In the teeth in which it was not apparent the infancy ring was considered to be at the junction of the two zones.

The infancy ring is accentuated by relatively mild systemic disturbances (fig. 10 *B*).

Hypoplastic Defects of the Infancy Ring: In hypoplastic teeth the infancy ring usually marks the limit of the hypoplastic zone occurring during infancy (fig. 12). It also represents the severest effect of the hypoplasia. It can be recognized grossly by its marked accentuation in the form of deep pittings and represents the most intense manifestation of the metabolic disturbance, as well as its abrupt termination.

About 5 per cent of the total of hypoplastic defects were acute and confined to the chronologic level of the infancy ring (acute hypoplasia of the infancy ring). They were usually of the pitted variety (Sarnat and Schour [16]). Such defects, of course, affect the first permanent molars and the anterior teeth, except the upper lateral incisors (fig. 12 and table 3).

Calcification During Early Childhood.—The period between the end of the first year and the end of the second year of life was considered to be the period of early childhood. Figures 6, 7 and 8 show the teeth and the levels which form during this period. Note that during this time the gingival third of the anterior teeth and the first permanent molars are forming. The bicuspids and second molars are just beginning their formation at the end of this period.

The dental tissues show, in general, calcification which is more homogeneous than that occurring during the infancy period but less homogeneous than that of the tissues calcified before birth.

The enamel formed during this time over the dentin cusps in the bicuspids and second molars is white, translucent and free from striae of Retzius. It has been called cuspal enamel [17] and compares in density with the rest of the enamel as mantle dentin compares with circumpulpal dentin (fig. 11). The cuspal enamel and the mantle dentin are normal and are not related to the chronologic development of the child.

The dentin forming and calcifying during this period shows a decrease in the incidence of interglobular dentin as compared with that in the infancy zone, but marbled or dappled dentin is common.

Hypoplasia of the Enamel: Recovery from hypoplastic defects of the infancy period is complete and abrupt at the beginning of the early

17. Noyes, F. B.; Schour, I., and Noyes, H. J.: Textbook of Dental Histology and Embryology, Philadelphia, Lea & Febiger, 1938.

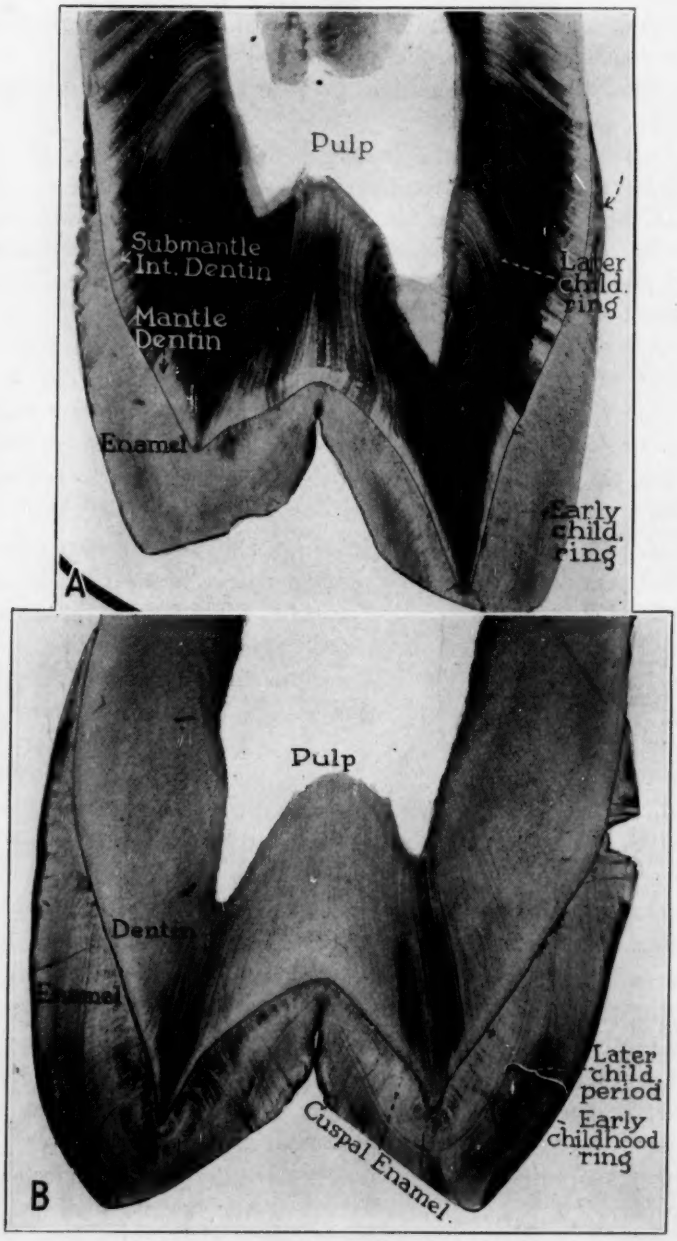

Figure 11

(See legend on opposite page)

childhood period (fig. 12). Chronic hypoplastic defects of the early childhood period are relatively rare.

Early Childhood Ring: A sharply accentuated ring can be observed in the permanent bicuspids and second molars at the level of the enamel and dentin forming at about 2½ to 3 years of age (fig. 11). The line is readily observed in the enamel, being present in about 75 per cent of the sections, but it is not so easily seen in the dentin, where it was observed in only about 25 per cent of the sections. It is also not so accentuated as the neonatal or infancy rings. Its histologic appearance in the enamel, and in the dentin also, is similar to that of the infancy ring. It probably represents a line of arrested growth.

Hypoplastic Defects of the Early Childhood Ring: About 5 to 10 per cent of all of the hypoplastic defects were confined to the level of the early childhood ring. These were acute and were generally smooth, whereas the acute hypoplastic defects of the infancy ring were generally deeply pitted (fig. 12).

Calcification During Later Childhood.—The period from the beginning of the third year to the end of the fifth year is usually designated as later childhood. The levels of the teeth forming and calcifying during this time are shown in figures 6, 7 and 8.

In general, the calcification after the third year is less homogeneous than that occurring during the early childhood period but better than that occurring during the infancy period. The enamel of the permanent teeth contains a distinctly greater number of incremental lines which are characteristically more heavily pigmented than those lines which occur at an earlier chronologic level. The dentin tends to exhibit a greater degree of interglobularity than that formed during the early childhood period but a lesser degree than that formed during the infancy period.

Hypoplasia of the Enamel: About 5 to 10 per cent of the total number of hypoplastic defects occur during this period and are of the chronic or multiple acute type. Clinically, they are usually seen only in the cuspids, the bicuspids and the second molars. In the incisor teeth the defects, when present, are confined to the area close to the cementoenamel junc-

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EXPLANATION OF FIGURE 11

Fig. 11.—Photomicrographs, *A*, of a permanent upper first bicuspid and, *B*, of a second bicuspid, showing the early childhood ring in the enamel at the chronologic level of 2½ years. The corresponding ring in the dentin cannot be seen. In *A* the later childhood ring is abnormally accentuated in the dentin at the chronologic level of about 5 years. Note that there is a corresponding disturbance in the contour of the enamel (arrow). The mantle dentin is the well calcified layer of dentin immediately under the enamel. The submantle interglobular layer of dentin lies immediately under the layer of mantle dentin. These two peripheral layers of dentin are normally present in all permanent teeth and are not related to the chronology of development. × 7.

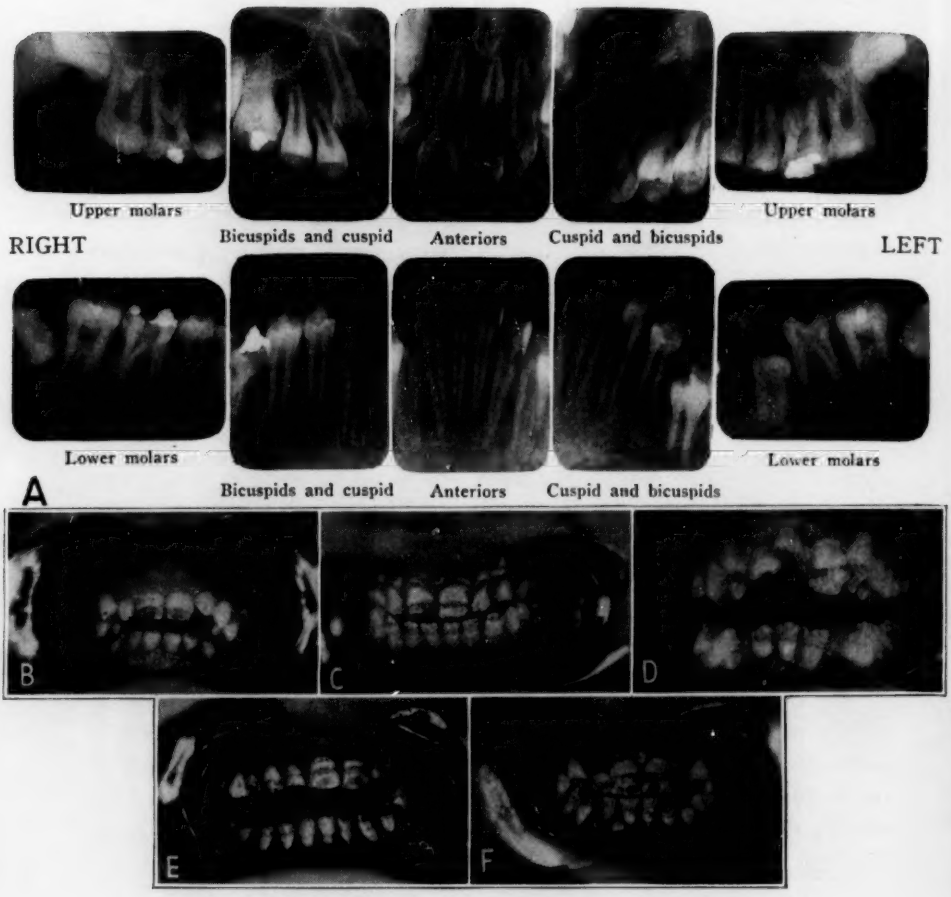

Figure 12

(See legend on opposite page)

tion, and in children they are generally covered by the gingival tissue and are therefore easily overlooked. The hypoplastic defects occurring during later childhood are generally of the smooth variety and give to the enamel a wavy appearance rather than the pitted appearance caused by those occurring during the infancy period. For this reason, too, they are often overlooked.

Later Childhood Ring: A ring is frequently present in the enamel of the bicuspids and second molars near the level of the cementoenamel junction and in the dentin of the roots of the other permanent teeth at a level that corresponds to the fifth year of life (figs. 6, 7 and 8). The ring was observed in the enamel of 80 per cent of the sections; it has the typical accentuation and appearance of a line of arrested growth. In the dentin the line is not markedly accentuated and was observed in only 60 per cent of the sections studied. Figure 11 *A* shows an accentuated later childhood ring in the dentin. Any accentuated incremental ring is as a rule more easily recognized in the enamel than in the dentin. The later childhood ring both in the enamel and in the dentin is less prominently accentuated than is the infancy or the neonatal ring.

EXPLANATION OF FIGURE 12

Fig. 12.—*A*, full mouth roentgenograms illustrating the most common type of enamel hypoplasia—chronic hypoplasia of the infancy period. Note the effect on the anterior teeth and the first permanent molars. The upper lateral incisors are not affected. The age period in which the hypoplasia occurred is, therefore, from birth to about 10 months of age. *B*, photograph illustrating chronic enamel hypoplasia of the infancy period. The hypoplasia is of a smooth variety. Note the abrupt termination and accentuation of the hypoplastic defect at the level of the tenth month (infancy ring). *C*, photograph illustrating enamel hypoplasia of the infancy period. Note that the incisal edges of the incisor teeth and the upper lateral incisor are unaffected. The age period at which the defect occurred is therefore from about the sixth to the tenth month (later infancy period). Note the abrupt termination and accentuation of the hypoplasia at the level of the infancy ring. *D*, chronic pitted enamel hypoplasia of the infancy period. Note that the upper lateral incisor is affected only at its incisal edge, while the other incisors show the effect in almost one half of their crowns. In this case tooth formation may have begun rather early and proceeded at a more rapid rate than in the average child. We consider this hypoplasia to have extended from birth to about 12 months of age. Note the prominent pitting at the level of the tenth month (infancy ring). *E*, multiple acute hypoplastic defects of the infancy and early childhood rings, well illustrated in the incisors. The upper lateral incisor is affected at the incisal edge and at the midcrown level. The acute hypoplasia of the infancy ring (tenth month) had a diffuse effect on the incisal third of the cuspids which were forming at that time. The effect of the hypoplasia at the level of the early childhood ring can be seen in the cuspal third of the bicuspids. *E*, chronic hypoplasia of the infancy and childhood periods. Note the effect on the upper lateral incisor. Note, too, the "recovery" effect during the early childhood period in the upper central incisors. (Permission to reproduce the roentgenograms and photographs in figure 12 was granted by Dr. B. G. Sarnat.)

Hypoplastic Defects of the Later Childhood Ring: As in the case of the infancy ring, the later childhood ring generally marks the termination of the chronic hypoplastic defects occurring during the preceding period. About 5 per cent of the total number of hypoplastic defects are of the acute type and are confined to the level of the later childhood ring. They usually are of the smooth variety and can be observed only in the gingival third of the cuspids, bicuspids and second molars (Sarnat and Schour [16]). Because these defects are smooth and represent a "wave" in the enamel, they often are overlooked.

Calcification During the Grade School Age.—The grade school age begins with the sixth year and continues until puberty. Enamel formation is being completed in the bicuspids and second molars but is just beginning in the third molars. The records during this period are therefore written in the dentin of the roots of the bicuspids and second molars and in the enamel of the third molars. Enamel formation in the third molars and root formation in the bicuspids are completed between the twelfth and the fifteenth year.

The beginning and the rate of formation of the third molar are inconstant. Its root formation is unpredictable. The result of any attempt to date the incremental pattern, therefore, can be only an approximation. Therefore, the dating of rings in the third molar will not be attempted until we have further studied the chronologic development of this tooth.

As previously indicated, rings are relatively more difficult to observe in the dentin than in the enamel. Therefore, the recording of rings in the teeth is virtually ended by the tenth year of life. However, the quality of the calcification from the eighth to the thirteenth year can be estimated in the root dentin of the bicuspids and second molars and the enamel and the dentin of the crown of the third molars.

The calcification of the dentin from the sixth to the thirteenth year is fairly homogeneous but not to a high degree. Dappled dentin is common, but markedly interglobular dentin is infrequent. The calcification, therefore, is better than that occurring during infancy and is comparable to that of the early childhood period.

The enamel of the third molars is well calcified, although striae of Retzius are common, except within the area of cuspal enamel.

The quality of the calcification of the dentin and enamel tends to decrease from the tenth to the thirteenth year. The dappling becomes more prominent in the dentin, and the incremental lines in the enamel are more frequent and more heavily pigmented. This decrease in the quality of the calcification is therefore characteristic of the prepuberal period.

Hypoplasia of the Enamel: Hypoplasia of the enamel, which could affect only the third molars during this period, was virtually absent in our material.

COMMENT

Prenatal Calcification.—The almost perfect calcification of the tissues calcified before birth is not surprising when one remembers that the embryo develops in an extremely well protected and favored environment. The embryo or fetus is a parasite, deriving all of its nourishment from the mother and drawing on her calcium reserves in the bones when necessary.

Mellanby,[7] Swanson [8] and Karnosh [9] have agreed that the calcification of the enamel formed before birth is better than that of the enamel formed after birth. However, their estimate of enamel formed before and after birth was relatively gross. Confirmation of this point was not possible until the discovery and establishment of the neonatal ring (Rushton,[18] Sachs [19] and Schour [10]), which demarcates clearly and easily the dentin and enamel formed before birth from that formed after birth.

On the basis of an analysis in which the Nicol prism method was used, Rushton [20] concluded that the calcification of the enamel formed before birth is not homogeneous and is not of a higher quality than that of enamel formed after birth by the same ameloblasts. There is a question in our minds whether the Nicol prism method does not analyze the crystalline arrangement of the precipitated salts rather than the quality or density of the calcification.

Hypoplastic defects in tissues calcified before birth are rare. Wolfe [21] and Maxwell [22] described several cases of fetal rickets in which there were marked disturbances in such tissues. In the 3 cases of hypoplastic defects in tissue calcified before birth which we have observed clinically the condition was probably caused by marked subnutrition of the mother during pregnancy.

In about 20 per cent of our material an accentuated ring was observed in the enamel and dentin at the chronologic level of about 7 months in utero. Sontag [23] also observed such a ring in bone. We have been unable to explain its existence.

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18. Rushton, M. A.: On the Fine Contour Lines of the Enamel of Milk Teeth, Dent. Rec. **53**:170-171 (April) 1933.

19. Sachs, J.: Histologische Untersuchung (Studien) des Zahnschmelzes unter Berücksichtigung der Milchzähne und besonderer Fälle, Thesis, Würzburg, 1933; cited by Wetzel, G.: Handbuch der Anatomie des Kindes, Munich, J. F. Bergmann, 1938.

20. Rushton, M. A.: The Birefringence of Deciduous Tooth Enamel Formed Before and After Birth, Brit. Dent. J. **67**:1-10 (July) 1939.

21. Wolfe, J. J.: Teeth in Fetal Rickets, Am. J. Dis. Child. **49**:905-911 (April) 1935.

22. Maxwell, J. P.: Two Cases of Foetal Rickets, J. Path. & Bact. **33**:327-338 (April) 1930.

23. Sontag, L. W.: Evidences of Disturbed Prenatal and Neonatal Growth in Bones of Infants Aged One Month, Am. J. Dis. Child. **55**:1248-1256 (June) 1938.

Neonatal Ring.—Rushton [18] and Sachs [19] reported the presence of a prominent contour line in the enamel formed at about the time of birth. Rushton [18] called it a "birth" line. Its physiologic significance and usefulness in dental investigative work, however, were not fully recognized until it was independently rediscovered by one of us (I. S.) in 1936 and named the neonatal line or ring.[10] The discovery was a by-product of an experimental analysis of the rate of growth of human enamel and dentin (Schour and Poncher [24]).

The neonatal ring has since been used as a biologic landmark in investigations on the rate of formation of human enamel and dentin (Schour and Massler [25]) and on the effects of neonatal trauma on the teeth (Schour and Kronfeld,[14] Kronfeld and Schour [26]).

The neonatal line is the result of the brief arrest in growth subsequent to birth and reflects the physiologic readjustments incident to birth. It is not surprising that the severe metabolic disturbances which the newborn infant experiences as it enters into the relatively less favorable extrauterine environment should leave their mark on the developing teeth. The loss in weight during the neonatal period and the temporary subnutrition are well known manifestations of the same change. Under ordinary conditions the newborn infant does not regain its birth weight until the end of the first ten days of extrauterine life.

Changes in bone during the neonatal period have been described (Harris,[13] Sontag [23]). Sontag [23] described a neonatal line in the round bones of the feet of infants. He found in some cases a "double" neonatal line in the long bones similar to that often observed in the teeth. The significance of the double effect is unknown.

Hypoplastic Defects: About 5 to 10 per cent of the population suffers from hypoplastic defects (Sarnat and Schour [16]). We estimate that about 70 per cent of all hypoplastic defects have their inception at birth and continue through the infancy period. About 2 per cent of these are acute and are confined to the neonatal period. They are seldom seen clinically, however, since the lesions are acute and are confined to the deciduous teeth. Hypoplastic defects occurring in the neonatal period can sometimes be seen at the cuspal tips of the first permanent molars. These are soon worn away.

That hypoplastic defects would occur at this time might be expected in view of the large number of pathologic conditions which constantly arise as a result of the trauma of birth.

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24. Schour, I., and Poncher, H.: The Rate of Apposition of Human Enamel and Dentin as Measured by the Effects of Acute Fluorosis, Am. J. Dis. Child. **54**: 757-776 (Oct.) 1937.

25. Schour, I., and Massler, M.: The Growth Pattern and Chronology of the Upper Deciduous Central Incisor, J. Dent. Research **16**:350 (Aug.) 1937.

26. Kronfeld, R., and Schour, I.: Neonatal Dental Hypoplasia, J. Am. Dent. A. **26**:18-32 (Jan.) 1939.

Pathologic accentuations of the neonatal ring depend on the severity of the adjustments during the neonatal period; they have been observed in cases of birth injury.[14] These accentuations may take the form of rings of greater width or deviations in the path of cellular activity, or they may be hypoplastic defects. Birth injuries of premature infants are particularly likely to produce hypoplastic defects of the neonatal ring (Stein[27]). In premature infants delivered normally the neonatal ring is found at an earlier chronologic level.

The neonatal ring is present at the characteristic level even in the teeth of children born by cesarean section, which indicates that normally the neonatal ring results from the change in environment rather than from the type of birth. Losch, Brown and Boyle[28] recently reported a greenish coloration of the neonatal ring in deciduous teeth obtained from a child who had a history of neonatal jaundice.

Calcification During Infancy.—That the calcification of the dental tissues is normally relatively poorer during the first ten months of life and that 70 per cent or more of all dental hypoplastic defects occur within this period (chronic hypoplasia of infancy) and usually cease suddenly thereafter are significant clinical observations for which an explanation should be sought by the pediatrician. They may indicate that the first ten months of life is a period during which the metabolism and the cellular activities are highly susceptible to constitutional disturbances.

Scammon[29] pointed out:

> From the standpoint of growth, practically all of infancy may be regarded as a transition period, in which the organs and structures of the body are departing, one by one, from the simple style of increment characteristic of the fetus to the diverse and complex modes of growth that obtain in childhood.

It is generally recognized by pediatricians that disease manifests itself differently during various age periods, largely because of the anatomic, physiologic and immunologic differences in various stages of development. In addition, the rapid rate of body growth which characterizes the early developmental periods, combined with these factors, may throw a strain on the assimilative functions of the body which would account for the frequency and the severity of nutritional disorders.

The rate of growth also influences the localization of the manifestations of disease. Thus, actively growing areas, such as the epiphysial

27. Stein, G.: Schmelzschäden am Milchgebiss und ihre klinische Bedeutung, Ztschr. f. Stomatol. **34**:843, 1936.

28. Losch, P.; Brown, J. C., and Boyle, P. E.: Staining of the Dental Structure in Jaundice of the Newborn, J. Dent. Research **19**:293 (June) 1940.

29. Scammon, R. E.: The Measurement of the Body in Childhood, in Harris, J. A.; Jackson, C. M.; Patterson, D. G., and Scammon, R. E.: The Measurement of Man, Minneapolis, University of Minnesota Press, 1930, p. 206.

ends of the long bones, are more apt to reflect diseases affecting growth (rickets, scurvy and syphilitic osteochondritis) than are the areas which grow slowly or not at all.

The frequency of rickets and tetany during infancy results also from the increased demand for calcium and phosphorus brought about by the rapid rate of growth. Eliot and Park [30] stated the problem succinctly:

> Rickets is dependent on bone growth. The disease in its manifest form cannot occur without growth of the skeleton, because lime salts cannot fail to deposit unless new-formed bone tissue exists for them to fail to deposit in. Rickets is present or absent according to the relationship between rate of lime-salt deposition and rate of bone growth. If the latter just corresponds to the former calcification of the bone is complete; if the latter exceeds the former, osteoid tissue makes its appearance and rickets develops.

Mellanby [7a] expressed the opinion that the decrease in the quality of the calcification is due to an increased rate of growth of enamel and dentin during the latter part of the first year. This is not true, since the most rapid rate of growth of enamel and dentin, as well as the best calcification, occurs prenatally. The rate of formation of enamel and dentin follows definite laws of growth gradients, whereas the calcification pattern proceeds irrespective of these rates and gradients of growth.

The fact that the enamel and dentin formed during the first three months of life show relatively better calcification than those formed during the subsequent six months suggests that the fetal mineral reserves have not yet been exhausted. A correlative fact well known to those practicing pediatrics is the relative freedom from rachitic manifestations during the first three months of life in spite of a vitamin D deficiency present since birth.

Infancy Ring: In describing certain regularly recurring and prominently accentuated lines of Retzius, which he stated might be caused by the decreased amount of sunshine during the winter months, Swanson [8a] stated:

> Broad incremental lines sometimes evident in the tips of the central incisors and in deposits of enamel of first molars which represent the accretions of about 1 year (corrected to about ten months) of age are possibly caused by nutritional disturbances associated with weaning.

Berten,[31] in 1895, and Asper [32] in 1916, described deficiencies in the formation and calcification of teeth at about the same chronologic level

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30. Eliot, M. M., and Park, E. A., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 1, chap. 36, p. 44.

31. Berten, J.: Hypoplasie des Schmelzes (congenitale Schmelzdefecte; Erosionen), Deutsche Monatschr. f. Zahnh. **13**:425-439, 1895.

32. Asper, H.: Ueber die "Braune Retzius'sche Parallelstreifung" in Schmelz der menschlichen Zähne, Schweiz. Vrtljschr. f. Zahnh. **26-27**:275, 1916-1917.

which they associated with the process of weaning. We cannot accept this interpretation, since the time of weaning varies while the infancy ring shows a high degree of constancy in the time at which it occurs. It also must be remembered that in modern times weaning is a gradual process, which often begins at birth. Yet the infancy ring is just as prominent today as in 1896, when the experience of weaning was more traumatic.

The infancy ring seems to demarcate the period of postnatal adjustments from the relatively more independent and robust existence of early childhood and thus may be compared with the neonatal ring as a critical point in the constitutional pattern of the developing child. Like the neonatal period, the tenth month is a period during which metabolic and cellular activities are acutely susceptibile to systemic disturbances. This is evidenced by the fact that the infancy ring is normally an accentuated incremental ring and that in the teeth of a patient who shows no clinical symptoms a severe and acute hypoplastic defect often occurs at the level of the tenth month.

It is likely that the infancy ring is a result of a profound adjustment in the internal conditions of the developing child about 10 months of age. In 1915 Robertson [6] reported the existence of a "critical period" in the latter half of the first year of the extrauterine development of man. The existence of this critical period was established on the basis of the observations of MacGregor [33] and has since been confirmed by the work of Thompson.[34] These investigators reported a decline in the growth curve at 6 to 12 months of age. The infant tends to become relatively underweight at the age of 7 to 10 months. This is not due to weaning. In addition, it was found that the incidence of certain diseases of infancy, such as diphtheria, cerebrospinal meningitis, measles, whooping cough and scarlet fever, was maximal between the ages of 6 and 9 months.

While the evidence presented by Robertson to support the existence of this critical period is not conclusive, it is at least provocative. In the light of the discovery of an infancy ring in the teeth which is formed during the same period, the problem merits further investigation.

Since the critical period falls at the link between two growth cycles, Robertson expressed the belief that it was due to a change from the metabolism of the first growth cycle to that of the second and therefore constituted a "physiologic" weaning process. A similar critical period was observed in the guinea pig at the junction of two growth cycles.

33. MacGregor, A. S. M.: Proc. Roy. Phil. Soc. Glasgow, April 21, 1909; cited by Robertson.[6]

34. Thompson, H.: Body Proportion in the Growing Infant, Growth **2**:1-12 (May) 1938.

While it is not difficult to explain the existence of the neonatal ring, the discovery of the possible underlying cause of the infancy ring presents a challenge to the pediatrician and the investigator of child growth which has not yet been met. It would not be surprising to find a corresponding ring in the long bones of normal infants of about 1 year of age.

Calcification During Early Childhood.—During early childhood, in contrast to infancy, the metabolic and cellular processes are relatively immune to systemic disturbances. Many patients who show no clinical evidence of improvement show a remarkable recovery in the calcification of the dental tissues as well as a relative immunity of the epithelial, enamel-forming cells. The recovery from the marked disturbance in the calcification and the formation of the teeth during infancy is abrupt and definite. The calcification of the teeth and the cells responsible for enamel formation, which were so highly sensitive during infancy even to subclinical systemic disturbances, now appear immune to disturbances which are clinically manifest.

Early Childhood Ring: The early childhood ring represents a chronologic level during which the metabolic and cellular activities were acutely susceptible to systemic disturbances. This is evidenced by the fact that the early childhood ring is normally more prominently accentuated than the other incremental rings formed during this period and by the increased incidence of hypoplastic defects in the enamel at this particular chronologic level.

Calcification During Later Childhood.—The decrease in the quality of the calcification and the higher incidence of hypoplastic defects in the enamel during the period from the third to the fifth year indicate an increased susceptibility of the dental tissues to metabolic and cellular disturbances. This susceptibility, however, is much less than during infancy, though greater than during early childhood.

Sarnat and Schour [16] have shown that there is no correlation between the exanthems (which occur during later childhood) and the hypoplastic defects which occur during infancy. The factors involved in the causation of the hypoplasia of the infancy period are still unknown. The increase in the incidence of hypoplastic defects in the enamel may, however, be related to the exanthematous diseases, which occur during this period. This problem merits further investigation.

Later Childhood Ring: The later childhood ring, like the early childhood ring, represents a chronologic level of acute susceptibility to systemic disturbance, as evidenced by the fact that it is normally accentuated and that about 5 per cent of all hypoplastic defects occur at this level.

The grade school age represents a period of improved calcification and decreased susceptibility to hypoplasia of the enamel.

Hypoplasia of the Enamel.—Hypoplastic defects in the enamel are pathologic accentuations of normal differences in the calcification pattern of the teeth. A study of the incidence of such defects therefore supplements the information derived from a purely histologic study of the quality and the degree of calcification of the teeth of normal persons.[14] Thus the greater incidence of chronic hypoplastic defects in the enamel during the infancy period is correlated with the poor calcification normally present in that period, while the acute hypoplastic defects occurring in the neonatal, infancy and early and later childhood periods represent only abnormal accentuations of normally accentuated incremental rings. In other words, the developmental periods are normally reflected only as zones of different calcification or accentuated incremental lines; in the case of subclinical or clinical disturbances these differences become accentuated in the form of chronic or acute hypoplastic defects.

From our material it appears that the same clinical condition affects the growth and the calcification of the dental tissues to different degrees, depending on the different developmental periods during which the clinical conditions are present.

RÉSUMÉ OF THE PHYSIOLOGIC AND PATHOLOGIC CHARACTERISTICS OF THE DEVELOPMENTAL PERIODS AS DEMONSTRATED BY THE RESPONSE OF THE ENAMEL AND DENTIN

Prenatal Period (4 months in utero to birth).—The formation and calcification of the prenatal tissue are normally good and are usually unaffected even by severe disturbances in the metabolism of the mother. Only severe deficiencies in the mother can affect the tissues calcified before birth.

Neonatal Ring (birth to 2 weeks of age).—The neonatal ring is probably an arrest line which is the result of the various factors concerned with the change from the intrauterine to the extrauterine physiology. Any trauma associated with birth tends to accentuate the neonatal ring in proportion to its severity.

Infancy Period (2 weeks to 10 months of age).—Calcification is normally not homogeneous during infancy and is easily affected even by subclinical disturbances in the metabolism of the growing infant. The activity of the epithelial enamel-forming cells is easily affected, so that hypoplastic defects in the enamel frequently result from disturbances which are not apparent clinically. This period is critical for the formation and calcification of the teeth.

Infancy Ring (about 10 months of age).—The infancy ring is probably an arrest line which normally results from the operation of unknown developmental physiologic factors in the 10 month old child.

It represents a critical period in which the formation and calcification of the enamel and dentin are acutely susceptible even to subclinical disturbances in the metabolism of the growing child. The susceptibility is even greater than during the infancy period, and the response in the enamel and dentin is even more manifest.

Early Childhood Period (about 10 months to 2½ years of age).—The formation and calcification of the enamel and dentin during this period are good, although not so good as during the prenatal period. It is a period of relative immunity to disturbances in the formation and calcification of the enamel and dentin, since disturbances in the metabolism of the growing child which are apparent clinically usually fail to affect the epithelial, enamel-forming cells (and no hypoplastic defects result) and cause only a relatively slight disturbance in calcification. The recovery in formation and calcification from disturbances operating during infancy is abrupt and complete.

Later Childhood Period (about 2½ to 5 years of age).—The calcification of the enamel and dentin is normally not so homogeneous as during early childhood, but it is better than during infancy. Disturbances in formation and calcification occur in response to disturbances in the metabolism of the growing child which are clinically manifest.

Grade School Period (about 6 to 10 years of age).—This period, like the early childhood period, is characterized by relatively good calcification and immunity to disturbances in enamel formation.

Early and Later Childhood Rings (about 2½ and about 5 years of age).—The early and the later childhood rings occur at the beginning and at the end of the later childhood period, just as the neonatal and the infancy rings demarcate the infancy period. They are probably the result of unknown developmental physiologic factors normally operating in the child at about 2½ and at about 5 years of age. They represent critical periods, in which the formation and calcification of teeth are acutely susceptible to disturbances in the metabolism of the growing child. The susceptibility is less than during the infancy period or at the tenth month of age but greater than during the later childhood period.

SUMMARY AND CONCLUSIONS

The human being goes through successive developmental epochs, each of which involves a complete, and often traumatic, change in metabolic, cellular and other constitutional processes. These are reflected accurately and permanently within the structure of the dental tissues forming and calcifying at the particular time. An analogy is found in the tree, of which the annual rings reflect the vicissitudes and variations in climate experienced during the period of growth. To the pedodontist, the pediatrician and others dealing with children, the quality of the

dental tissues should serve as a valuable index of the prenatal care of the mother and of the feeding of the child during infancy and childhood.

Over 1,000 human deciduous and permanent teeth were studied in ground and decalcified sections for the purpose of evaluating the degree of calcification of the enamel and the dentin at different ages. The calcification pattern of the teeth, which is indicated in table 3 and in figures 6 and 7, is a direct reflection of the physiologic characteristics of the developmental periods of the growing child. In addition, a clinical examination of the teeth of children was made, with emphasis on the incidence of acute and chronic hypoplastic defects in the enamel.

The period in which there are the greatest susceptibility to hypoplastic defects in the enamel and the poorest calcification lies between birth and about 10 months of age. Deficiencies in calcification tend to become progressively accentuated at about 10 months of age, when a crisis occurs and the recovery in calcification (as evidenced by the amount of interglobular dentin and hypoplasia of the enamel) is abrupt and complete. Periods of acute susceptibility to metabolic and cellular disturbances (evidenced as acute deficiencies in formation and calcification) occur at the neonatal period and at the ages of 10 months (infancy ring), about 2½ years (early childhood ring) and about 5 years (later childhood ring). The recognition of the constitutional basis for the susceptibility to defects in calcification and formation which occur during the infancy period and at the levels of the infancy and the early and later childhood rings awaits further investigation.

A similar histologic analysis of the calcification pattern of the bone would probably reveal that it also reflects the developmental epochs of the growing child.[35] Sontag has already revealed the presence of a neonatal line in the bones such as we have seen in the enamel and dentin. There are indications that in bone the calcification occurring before birth differs from that occurring after birth.

The elucidation of the calcification pattern of human teeth is valuable only in so far as it can be correlated with physiologic and clinical observations, which we have been able to accomplish only to a limited degree. It is hoped that in the future the pediatrician and the endocrinologist may offer such correlations.

35. Recently, further evidence of deficient calcification during infancy has been found in the bones of normal children by Robinson (Study of Two Hundred and Forty Breast-Fed and Artificially Fed Infants in St. Louis Area: Comparison of Prophylactic Antirachitic Effects of One Hundred and Thirty-Five and Two Hundred Unit Irradiated Evaporated Milks, Two Hundred Unit Irradiated Fresh Milk and Human and Nonirradiated Evaporated Milk Fortified with Eight Hundred to One Thousand Units of Vitamin D as Viosterol, Am. J. Dis. Child. **59**:816-827 [April] 1940). She examined the roentgenograms of the wrists of 240 healthy infants and found evidence of rickets in 60.8 per cent. Of these, 33 per cent showed positive and 27.8 per cent showed "questionable" evidence of rickets.

EXTREME EOSINOPHILIA AND LEUKOCYTOSIS

AN UNUSUAL CLINICAL SYNDROME OF UNKNOWN ORIGIN OCCURRING IN CHILDHOOD

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The purpose of this communication is to call attention again to a peculiar syndrome occurring in childhood and characterized by unexplained eosinophilia of marked degree, considerable increase in the total white cell count and general adenopathy with or without splenomegaly persisting over long periods. I have encountered 3 patients with this condition, on 2 of whom I have already published reports. I wish to report here the final outcome in the case of my second patient, who was reported on in 1931 but was followed up for seven years thereafter, and to report the case of a third patient, whom I have had under observation for the past year and a half.

SUMMARY OF TWO PREVIOUSLY REPORTED CASES

In 1925, under the title "Unusual Eosinophilia with Splenomegaly (Eosinophilic Leukemia?) in a Child Aged Six Years," [1] I reported my first case. During the two and a half months the patient in this case (a girl) was under observation she had moderate enlargement of the spleen, slight general adenopathy and leukocyte counts varying between 14,800 and 25,600 per cubic millimeter. The proportion of eosinophilic cells varied between 39 and 70 per cent and almost all of them were of the adult type. The child contracted pertussis and bronchopneumonia, of which she quickly died. An autposy was not performed.

In 1931 I published in the AMERICAN JOURNAL OF DISEASES OF CHILDREN [2] the report of a second case, in which a more complete study was carried out, in the pediatric service at Mount Sinai Hospital. A summary of the data in that case follows.

CASE 2.—Pablo V., an 8 year old Puerto Rican boy who had been in the United States for one month, was admitted to the hospital on Nov. 21, 1929 with complaints of vomiting and alternating diarrhea and constipation. For many years the boy

From the Pediatric Services of Mount Sinai Hospital and the Hospital for Joint Diseases.

1. Bass, M. H.: Am. J. M. Sc. **170**:416 (Sept.) 1925.

2. Bass, M. H.: Eosinophilic Leukemia: Case in Child Aged Eight Years, Am. J. Dis. Child. **41**:1394 (June) 1931.

had had a chronic nonproductive cough. Examination revealed that he was pale and thin, weighing 42 pounds (19.1 Kg.). A few pea-sized, shotty lymph nodes were present in both axillas and groins. Numerous rhonchi were heard; they were most abundant over the bases of both lungs posteriorly. A soft systolic murmur was heard best over the third left interspace. This was not transmitted. The liver and the spleen were not palpable. The Pirquet test gave a positive reaction. Urinalysis gave normal results. The temperature was normal.

The patient had persistent leukocytosis, the cell counts ranging between 24,000 and 45,200, with the proportion of mature eosinophils varying between 33 and 73 per cent. The coarse rales were constantly present, and the roentgen examinations consistently showed miliary pulmonic infiltrations. Two determinations of the basal metabolic rate gave the values of + 31 and + 48 per cent. All investigations relative to the cause of the eosinophilia, including examination of the stools for ova and parasites, cutaneous tests with protein and complement fixation and

TABLE 1.—*Results of Blood Counts in Case 2*

Date	Hemoglobin Content, per Cent	Red Cells, per Cu. Mm.	White Cells, per Cu. Mm.	Platelets, per Cu. Mm.	Polymorphonuclear Neutrophils, per Cent	Eosinophils, per Cent	Basophils, per Cent	Lymphocytes, per Cent	Mononuclear Leukocytes, per Cent
11/27/29	65	3,720,000	36,000	350,000	16	68	1	13	2
12/ 2/29	..	.....	26,400	.....	49	33	..	15	3
12/ 7/29	52	.....	32,000	.....	26	45	1	25	3
12/31/29	54	3,380,000	24,200	155,000	18	58.5	..	20	3.5
1/27/30	50	3,250,000	40,300	280,000	14.5	72.5	..	10.5	2.5
2/17/30	50	.....	45,200	.....	18	66	..	15	1
4/19/30	47	3,600,000	40,000	280,000	22	68	..	10	..
5/15/30	60	.....	31,000	.....	19	41	..	40	..
8/15/30	60	.....	24,000	.....	5	70	..	20	5
9/15/30	57	3,600,000	27,000	250,000	12	73	..	12	3
10/13/30	73	.....	28,600	.....	19	60	..	17	4
11/15/30	..	.....	20,000	.....	14	60	..	20	6
10/13/31	45	.....	16,400	.....	31	43	1	16	9
3/24/32	75	4,600,000	17,400	250,000	40	14	..	40	6
11/26/32	74	3,900,000	6,300	.....	38	17	0.5	35	9.5
11/ 4/37	100	5,500,000	10,000	392,000	45	4	..	44	7

cutaneous tests for Echinococcus, yielded negative results. A biopsy of sternal marrow showed myeloid hyperplasia with a preponderance of eosinophils.

The boy has subsequently been observed both in the hospital ward and in the follow-up clinic. On Oct. 13, 1930 he was again admitted to Mount Sinai Hospital with a complaint of an infection of the upper respiratory tract of ten days' duration, persistent cough, low grade fever and a cutaneous eruption. Examination showed an eruption, limited to the lower half of the abdomen, which consisted of many light reddish papular areas varying only slightly in size, most of them being about the size of a split pea. The surface of these lesions was somewhat striated, and the margins blended rather smoothly into the adjacent tissue. There was no surrounding erythema. Many of the papules showed some tendency to become confluent. This tendency was most pronounced in the lesions above the pelvis. The rash did not fade entirely on pressure, although it became considerably lighter.

Generalized lymphadenopathy was noted, most marked over the upper half of the body, that is, around the axillas and the neck, especially along the sternocleidomastoid muscle. The glands were small, freely movable and not tender. They showed no tendency to become confluent or to suppurate. The liver and the spleen were not palpable. Occasional crackling rales could be heard over the

base of the right lung posteriorly. The heart was normal. Urinalysis occasionally revealed a faint trace of albumin. Blood counts showed 60 per cent eosinophils (table 1). Two determinations of the basal metabolic rate gave the values of + 43 and + 33 per cent.

Roentgen examination of the chest on November 1 showed persistence of the fine, pinhead-sized shadows scattered throughout the lungs. It was noted that the shadowed areas were present mainly in the bases of the lungs and that there was definite evidence of diminution in their density and extent as compared with their appearance in the roentgenograms taken during the first stay in the hospital.

On November 3 the child was on the play roof, from which he was brought down at 2:30 p. m. in a state of collapse. The respiration was difficult and labored. Asthmatic breathing, with an expiratory wheeze, was noted. The liver was palpable 3 fingerbreadths below the free costal border and was tender. The boy was given 7 minims (0.46 cc.) of epinephrine hydrochloride (1:1,000) and improved rapidly. At 4 p. m. he had another attack, which was also relieved by epinephrine.

The boy was discharged from the hospital on November 11, having had no further attacks of asthma and the cutaneous lesions, which had been diagnosed as erythema multiforme, having improved. He was subsequently seen in the follow-up clinic at Mount Sinai Hospital; he recovered gradually and completely (table 1). Roentgenograms of the chest taken March 24, 1932 and June 7, 1934 were normal, the small infiltrative shadows having completely disappeared. The eosinophilia gradually disappeared, as did the leukocytosis, though only in the course of a number of years. When the patient was last seen, nine years after his first admission, the proportion of eosinophils was only 1 per cent, and the total white cell count was 12,000. He was in excellent health.

REPORT OF AN ADDITIONAL CASE

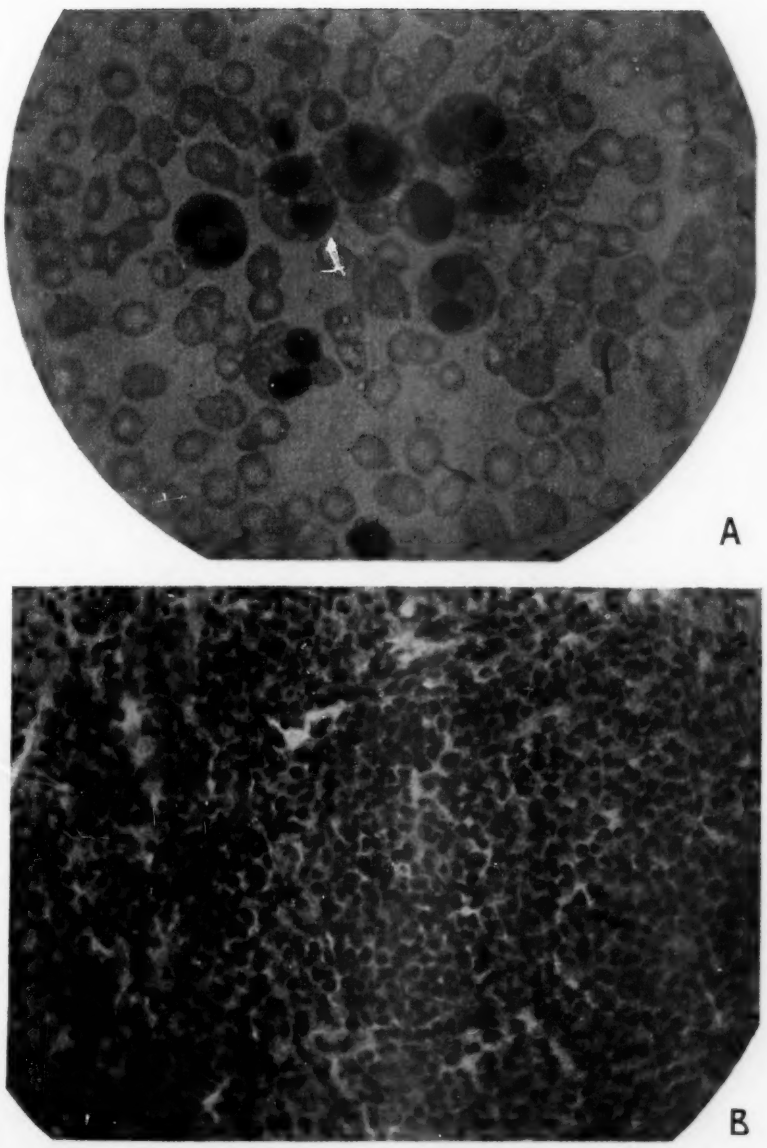
In the case of a third patient (hitherto not reported on) the same clinical characteristics were present. This patient has been under observation for the past eighteen months. His history follows.

CASE 3.—John D., a Negro boy aged 6½ years, was admitted to the Hospital for Joint Diseases in the orthopedic service of Dr. I. Zadek on March 7, 1939. He was sent to the hospital for operative correction of bilateral knock knee.

History.—He was 1 of a family of 7 children, all living and well. There was no history of syphilis or tuberculosis in the family. He was born after a pregnancy of seven months. His birth weight was 5 pounds (2,268 Gm.). He first received cod liver oil at the age of 9 months, and it was administered sporadically thereafter. The feeding of fruit juice was begun when he was 3 months old. There was no history of serious illness, though he had been subject to many head colds and had enuresis.

About one year before admission his mother noted a knock knee deformity, which had been getting progressively worse. He was able to run and play like other children but recently had begun to complain of pain and tenderness in his knee.

Physical Examination.—On admission, physical examination showed a fairly well nourished boy with definite evidence of rickets. His most striking feature was his curiously narrowed and elongated head, an example of extreme dolichocephaly. There were a definite Harrison groove and a rachitic rosary. The



A, smear of peripheral blood (case 3), showing the adult type of eosinophilic cells in the circulating blood. *B*, section of axillary lymph node stained with hematoxylin and eosin (case 3), showing the enormous infiltration with eosinophilic cells.

UNIV. OF MICH.

epiphyses of the wrists and the distal ends of the tibias and fibulas were enlarged. Both feet were moderately flat. The knees, especially the right, had marked varus deformity. There was no deformity of the spine. The upper extremities were normal.

The eyes, ears, skin and lymph nodes were normal. The throat was pale, but the tonsils were large and cryptic. The heart and lungs were normal. The abdomen was soft, and the liver and spleen were not palpable. The genitals were normal. Roentgen examination showed no evidence of active rickets. The outer condyles of the femurs were more dense than the inner. A roentgenogram of the skull was normal.

Laboratory Data.—Examination of the urine showed a specific gravity of 1.028, a neutral reaction, no sugar, acetone or albumin and a normal sediment.

A blood count (table 2) revealed moderate anemia and 6 per cent eosinophils. The Wassermann and Kahn reactions of the blood were negative.

TABLE 2.—*Results of Blood Counts in Case 3*

Date	Hemoglobin Content, Gm. per 100 Cc.	Red Cells, per Cu. Mm.	White Cells, per Cu. Mm.	Platelets, per Cu. Mm.	Segmented Neutrophils, per Cent	Nonsegmented Neutrophils, per Cent	Eosinophils, per Cent	Basophils, per Cent	Lymphocytes, per Cent	Mononuclear Leukocytes, per Cent
3/ 8/39	9.8	4,160,000	17,300	.....	70	4	6	..	19	1
4/ 4/39	8.8	4,800,000	16,500	.....	59	3	22	1	15	..
4/12/39	10.2	4,160,000	38,300	192,000	29	1	58	..	11	..
4/14/39	....	.....	43,000	.....	12	2	77	..	9	..
4/19/39	10.0	4,200,000	50,000	300,000	5	..	73	1	20	1
4/20/39	9.2	4,320,000	51,200	.....	7	..	70	..	18	1
4/25/39	10.0	4,000,000	33,000	.....	7	..	84	1	4	..
5/ 1/39	9.6	4,160,000	22,000	.....	21	3	52	..	21	1
5/10/39	11.0	.....	30,000	.....	17	..	57	..	33	3
5/17/39	10.0	4,640,000	18,900	.....	16	..	58	..	25	1
5/21/39	....	.....	28,000	.....	13	..	56	2	20	9
5/24/39	9.4	4,480,000	26,800	.....	20	..	55	..	24	4
6/ 1/39	10.2	4,000,000	34,900	.....	10	2	80	..	8	..
7/24/39	8.3	3,994,000	8,750	.....	33	..	35	..	28	4
1/24/40	...	.....	.....	.....	21	3	42	..	29	5
6/22/40	...	.....	.....	.....	16	..	53	2	29	..
1/ 3/41	9.8	4,640,000	9,400	.....	30	2	29	1	37	1

Determinations of the chemical constituents of the blood showed 10.3 mg. of calcium per hundred cubic centimeters, 3.4 mg. of inorganic phosphorus, 15.1 Bodansky units of phosphatase, 90 mg. of sugar, 23 mg. of nonprotein nitrogen, 204 mg. of cholesterol and 142 mg. of cholesterol ester.

Course.—It had just been decided to perform a supracondylar osteotomy of both femurs when the boy contracted an infection of the upper respiratory tract; he had elevations of temperature to 100 F. every day for a week. For this reason he was not operated on and was discharged from the hospital on March 13.

Second Admission.—The patient was readmitted to the hospital on April 4, at which time it was thought that an infection of the tonsils might be responsible for the fever. However, Dr. L. Glushak, of the nose and throat department, noted a marked eosinophilia and referred the boy to the pediatric service. When I saw him for the first time leukocytosis was still present and there were 22 per cent eosinophils. During the period of observation the patient's temperature ranged up to 102 F. The spleen became definitely palpable, 1 fingerbreadth below the costal margin. Many lymph nodes became palpable in the neck, axillas and groins; some were as large as marbles, discrete and not tender. The blood pressure

was 90 mm. of mercury systolic and 62 mm. diastolic. A roentgenogram of the chest was normal. Reaction to Pirquet and Mantoux tests with 1: 10,000 and 1: 1,000 dilutions of old tuberculin were negative. The heterophile antibody reaction was negative. Urinalyses gave normal results. Careful inquiries relative to the usual causes of eosinophilia all yielded negative results. Numerous examinations of the feces were negative for ova and for parasites. There were no signs or symptoms of trichinosis. There was no familial or personal history of allergy.

The boy seemed to feel well, had no complaints and ate and slept well. The bowel action was regular. In spite of this he had a continuous low grade fever and leukocyte counts of over 51,000, with the proportion of eosinophils as high as 84 per cent.

Examinations of Blood and Bone Marrow.—From several examinations of the blood and the bone marrow by Dr. Carl Reich, the hematologist of the hospital, the following data were obtained:

The sedimentation rate was 8 mm. in one hour, the coagulation time five minutes, the bleeding time two minutes and the clot retraction time one and one-half hours. There was no sickling of the red cells; the blood group was 2. The total cell count for a specimen of bone marrow, obtained by sternal puncture, was 160,000. The differential count showed 20 per cent polymorphonuclear eosinophils, 8 per cent band eosinophils, 24 per cent eosinophilic myelocytes, 10 per cent polymorphonuclear neutrophils, 8 per cent band neutrophils, 7.5 per cent neutrophilic myelocytes, 0.5 per cent myeloblasts, 4.5 per cent monocytes, 4.0 per cent lymphocytes, 10.5 per cent erythroblasts and 1.0 per cent proerythroblasts.

Biopsy on Lymph Node and Muscle.—The report of a biopsy on an axillary lymph node and a piece of pectoral muscle, performed by Dr. Henry L. Jaffe, pathologist, was as follows:

"The specimens consist of a small piece of pectoral muscle and a small, oval, firm lymph node, which is about 1 cm. in its greatest diameter. In one section of the lymph node there are numerous cloudy small yellowish nodules, 1 to 2 mm. in diameter.

"Microscopic Examination: The muscle fibers show no signs of trichinosis.

"The normal architecture of the lymph node has been modified but not altogether replaced. Occasional cortical follicles with germinal centers and also anastomosing medullary cords are present.

"The conspicuous feature is the large numbers of eosinophilic leukocytes within the lymph sinuses and, to a lesser extent, within the medullary cords. These leukocytes tend to be clumped in large and small aggregates. Most of them appear to be segmented polymorphonuclear cells, but there are a few staff cells and young forms. In some areas the eosinophils are massed together in sheets, crowding out the other cells. A moderate number of eosinophilic leukocytes are also noted within the connective tissue of the hilus and of the capsule of the node. They are likewise observed within blood vessels (and this is reflected in the blood count). Dispersed between the eosinophils in the sinuses are numerous cells with large nuclei which resemble reticulum cells."

Tonsillectomy.—Since the boy had shown no signs of hemorrhage, even when the specimen for biopsy was obtained, and the tonsils seemed definitely diseased, tonsillectomy was performed by Dr. Glushak. The operation was carried out without difficulty, and there was no bleeding either during or after it.

Examination of Tonsils.—The report of the pathologist on the examination of the tonsils was as follows:

"The specimen consists of a pair of tonsils, each measuring 3 by 1.5 by 1 cm. Microscopic examination shows lymphoid hyperplasia, with prominence of the germinal centers; the muscle and the connective tissue are infiltrated by eosinophilic polymorphonuclear leukocytes."

Course After Second Discharge.—The boy was discharged from the hospital on June 3 and followed up in the outpatient department. Numerous blood counts were done, and the results are given in table 2. He was last seen on Jan. 3, 1941, at which time it was noted that he had been in excellent health and had attended school regularly. There had been no regrowth of tonsillar tissue. The cervical and axillary lymph nodes were still palpable, though they were smaller, and the spleen was felt 1 fingerbreadth below the costal border. The basal metabolic rate was normal.

Comment on the Case.—It is of interest that the child's blood was first examined when no symptoms except slight fever were present. At that examination the proportion of eosinophils was only 6 per cent. Apparently, we had the good fortune to obtain this count at the very beginning of the disease.

COMMENT

The question arises as to how to classify such cases. The excessive eosinophilia does not seem to be due to any of the usual causes, which I believe have been ruled out. Intestinal parasites, trichinosis and Hodgkin's disease were definitely excluded. In case 2, in which the patient recovered, there were two short attacks of asthma-like paroxysms, which, though severe, never recurred. Roentgenographically this child showed marked pulmonary changes, which may have had some bearing on the attacks. I do not believe that the two transitory attacks, which occurred on the same day, can stamp the entire disease as allergic, for the eosinophilia persisted for many years, during which time no other symptoms of allergy were observed.

With regard to the differential diagnosis, it is to be noted that in cases of periarteritis nodosa the blood may have characteristics similar to those in my cases. Spiegel,[3] in a review on periarteritis nodosa, said:

> Though leukopenia is occasionally present, leukocytosis is far more usual, counts of 40,000, 56,000 and 66,000 having been encountered relatively frequently. Such high leukocytosis is otherwise rare, sometimes occurring in lobar pneumonia.
>
> The predominant cell type is the polymorphonuclear leukocyte, to the extent of 96 per cent. Striking eosinophilia has occurred in a minority of instances, the count being 23 per cent in Lamb's first case, 79 per cent in Strong's case and 18 per cent in our case 16. The eosinophilia may be transient, and it may disappear when some surgical complication occurs.

Neither the symptoms nor the results of histologic examinations in my cases suggested periarteritis nodosa.

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3. Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993 (Dec.) 1936.

Hodgkin's disease may at times be associated with a high eosinophil count.[4] This may occur not only in the case of adults but in the case of children, such as that of a 14 year old boy reported by Kato and Cardozo.[5] These authors cited instances of white cell counts as high as 100,000, of which 72 to 90 per cent were eosinophils. Neither the histologic sections nor the clinical course in my cases showed a resemblance to those in cases of Hodgkin's disease.

Not only the enormously high eosinophil count, but the increase in the total of white cells differentiates my cases from others. Few diseases are characterized by such high white cell counts and an apparent absence of symptoms. In case 3 (that of John D.), the patient was perfectly happy and ate and slept like a normal child; yet he had a temperature around 101 F. and a count of over 51,000 leukocytes.

Another condition which must be excluded in arriving at a diagnosis in these cases is familial eosinophilia. In my first case blood counts for other members of the patient's family were not available. The second case was that of a Puerto Rican boy whose family was not in this country. In my third case the patient, an American-born Negro, was 1 of a family of 7 children. Examinations of the blood of the mother and of all of the siblings failed to show eosinophilia.

In this connection must be mentioned a case reported by Atmar,[6] in August 1940, under the title "Familial Eosinophilia." The patient, a Mexican woman of 29, while afebrile had a white cell count of 30,000, of which 70 per cent were eosinophils. All of the cells were of the mature variety. There was no lymphadenopathy, and no mention was made of enlargement of the liver or the spleen. Roentgen study of the lungs showed "considerable cloudiness and increased density in both lower lobes." At operation for umbilical hernia and displaced uterus it was noted that the surface of the liver was studded with white areas, 0.5 to 1 cm. in diameter, which biopsy showed were due to dense infiltration with eosinophilic cells. Three of her 4 siblings showed marked eosinophilia, as did her 2 children. After fifteen months' observation the total white cell count had fallen from 42,700 to 8,800, but the proportion of eosinophils was still 29 per cent. Exactly what relation such a clinical picture bears to the syndrome I am describing is not clear.

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4. Major, R. H., and Leger, L. H.: Marked Eosinophilia in Hodgkin's Disease, J. A. M. A. **112**:2601 (June 24) 1939.

5. Kato, K., and Cardozo, W. W.: J. Pediat. **12**:165 (Feb.) 1938.

6. Atmar, R. C.: Familial Eosinophilia: Report of Case with Biopsy of Liver, J. A. M. A. **115**:449 (Aug. 10) 1940.

There is a group of unusual cases with varying symptoms reported under the title "Eosinophilic Leukemia."[7] In these cases the outcome was fatal, and the disease resembled genuine leukemia in that the spleen was hugely enlarged, the number of leukocytes was greatly increased (up to 236,000 cells per cubic millimeter) and there was a tendency to hemorrhage. The differential count revealed a preponderance of eosinophilic cells. Opinions have differed as to the classification of these cases with regard to the nature of the disease; some authors favor their inclusion among the cases of leukemia, while others have expressed the belief that they are instances of infections of various types. Until 1939 only occurrences of the disease in adults had been reported. However, a case reported from Copenhagen by Thomsen and Plum[8] is of particular interest because it is that of a boy aged 11 years. The illness in this case was immediately preceded by an attack of acute tonsillitis, after which examination showed:

> A white cell count of 45,000-65,000, of which 70-90% were eosinophils of an abnormal, partly immature type, moderate anemia and very great enlargement of the spleen. . . . The bone marrow showed a pronounced leukemic picture with an enormous increase in the number of eosinophil elements, besides a large number of "stem" cells of a type not described previously.

After temporary relief due to roentgen treatment, the cervical nodes became enormously swollen, and the patient was readmitted to the hospital. "By this time the hematological picture had changed completely, being dominated by typical myeloblasts which gradually made up the majority of the white cells, while the abnormal eosinophils had disappeared." The hemoglobin content had dropped to 22 per cent, and in spite of transfusions the boy died, about one year after the onset of the disease. I think that the authors are right in reporting this case under the title "Eosinophilic Leukemia." The eosinophilic cells were of an abnormal, partly immature type, which at once differentiates the disease from that in the cases I am reporting, since in them the eosinophils were all of the mature adult type.

However one may, rarely, encounter cases in which there is pronounced leukocytosis with extreme eosinophilia, only normal adult forms of white cells are present in the circulating blood and the disease progresses rapidly to a fatal outcome. Such was the case of a patient who was studied in New Haven Hospital in the service of Dr. G. Powers, who has given me permission to report the case.

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7. Stephens, D. J.: Am. J. M. Sc. **189**:387 (March) 1935. Forkner, C. E.; Teng, C. T.; Ch'u, Y. C., and Cochran, W.: Chinese M. J. **51**:609 (May) 1937. McCowen, G. R.; Parker, H. B., and Panton, P. N.: J. Roy. Nav. M. Serv. **18**:131 (April) 1932.

8. Thomsen, S., and Plum, P.: Acta med. Scandinav. **101**:116, 1939.

A 2½ year old white girl, born and brought up in New London, Conn., was admitted to the New Haven Hospital in September 1935. Birth and the neonatal period were normal; she was breast fed until the age of 2 years, but the feeding of solids was begun when she was 1 year old. Except for occasional infections of the respiratory tract and mild diarrhea at the age of 1 year, she was healthy until the present illness began. Five months before admission her gums became swollen and tender and pus could be expressed from them. (Siblings had had a similar condition at the same age.) Local treatment improved the gums. A month later she vomited for a week; a physician observed that the spleen was enlarged. After the attack of vomiting the child complained of pain around the umbilicus after meals, and the abdomen became more prominent. Four weeks before admission diarrhea, with occasional streaks of fresh blood in the stools, developed. For the past month she had had a loose cough and had occasionally been short of breath during the night. Since the onset of diarrhea there had been a loss in weight of about 8 pounds (3.6 Kg.).

On examination the child seemed chronically ill but not markedly anemic; there was an occasional loose cough. The upper anterior deciduous incisors showed marked disintegration; The lower series were stained, but the enamel appeared normal. There were small, shotty lymph nodes in the neck, the axillas and the groins. The lungs were clear and the heart was normal. The abdomen was distended and soft; the edge of the liver was felt 6.5 cm. below the costal margin in the midclavicular line; the spleen was smooth and firm, and the tip was 8 cm. below the costal margin in the left anterior axillary line. There were no hemorrhages in the skin, mucous membranes or fundi.

On admission the red cells numbered 3,210,000 and the white cells 54,000; the hemoglobin content was 65 per cent (9.4 Gm. per hundred cubic centimeters). The reticulocytes numbered 4.3 per cent. The differential count (fixed smear) showed 18 per cent neutrophils, 56 per cent eosinophils, 3 per cent basophils, 17 per cent lymphocytes, 2 per cent monocytes, 4 per cent neutrophilic myelocytes and 1 per cent normoblasts. Examination using the supravital staining method showed 17.5 per cent neutrophils, 60 per cent eosinophils, 0.5 per cent basophils, 15 per cent lymphocytes, 4.5 per cent monocytes and 2.5 per cent unclassified cells. There were 230,000 platelets. The bleeding time and the clotting time were normal.

A study of sternal marrow by the supravital staining method showed it to be predominantly myeloid, and the elements present were of the late stages in the myelocyte series. There was a distinct increase in the number of eosinophils (20 per cent).

The eosinophils in the peripheral blood were adult if judged by the nuclei, which were multilobed; the cytoplasm was not normal, for many cells showed granules in a small area, while the rest of the cytoplasm appeared pale gray. The blood picture remained essentially unchanged during ten days' observation.

Fecal examination revealed occult blood but no ova or parasites. The spinal fluid was normal.

Roentgenograms of the long bones and the skull were reported normal. A roentgenogram of the chest showed parenchymatous mottling of both pulmonary fields.

The child left the hospital on September 29. She was seen once after discharge, and examination at that time showed that the red cells and the hemoglobin content had decreased and the platelets numbered 190,000 and the white

cells 90,000, of which 54 per cent were eosinophils. About six weeks after leaving the hospital the child died. Autopsy was not permitted.

It is greatly to be regretted that autopsy could not be performed in this case, for the clinical picture appears to be midway between that of true leukemia and the symptom complex on which I am reporting. The great enlargement of the spleen and liver, the general adenopathy, the marked leukocytosis, the increase in the proportion of eosinophils to 60 per cent, the adult type of the white cells and, finally, the results of roentgen examination of the lungs are striking. However, without the report of an autopsy, Hodgkin's disease cannot be excluded.

When, in 1931, I reported my second case, I thought the disease most resembled leukemia and therefore entitled the report "Eosinophilic Leukemia." However, over a period of six years the child made a complete recovery. This fact in itself is enough to take the disease out of the category of genuine leukemia. The patient in my third case, whom I have had under observation for a year and a half, is now in excellent physical condition and without leukocytosis, though the eosinophilia persists. I feel that the disease in this case also must be construed as falling outside of the classification of genuine leukemia. My 3 cases resemble one another, and in each I received the impression that the patient was suffering from some type of chronic infection.

Recently I read a report of 4 cases by Valledor, Mendoza and Pedrera [9] in Habana, which are of considerable interest in this connection. The patients in these 4 cases were carefully studied over a long period. They were all children between the ages of 2 and 11 years. In 3 cases the illness was characterized by fever which lasted three to six months, and in 1 the course was afebrile. General lymphadenopathy was present in all 4 cases and slight enlargement of the liver and the spleen in 3. A constant feature of the disease was persistent leukocytosis, lasting several months; the white cell counts ranged from 20,000 to 70,000, figures out of all proportion to the apparent mildness of the illness. Accompanying this was extraordinary eosinophilia; in 1 case 81 per cent of the white cells were eosinophils. In all 4 cases there were diffuse miliary shadows in the lungs, which disappeared as the patient recovered, as they all did. The total white cell count returned to normal months before the disappearance of the eosinophilia, which persisted in some cases for several years. Biopsy of lymph nodes showed hyperplasia and infiltration with many polymorphonuclear eosinophilic cells. In all 4 cases there was infection with Trichocephalus and in 1 with Ascaris also. However, the successful removal of the parasites had no

9. Valledor, T.; Mendoza, R., and Pedrera, J.: Bol. Soc. cubana de pediat. **11**:207 (May) 1939.

influence on the course of the disease. The Cuban authors expressed the belief that the disease in their cases was some form of chronic infection and gave reasons for excluding the diagnosis of leukemia.

I believe that the disease in my 3 cases and that in the 4 cases reported by Valledor, Mendoza and Pedrera were the same. The hematologic, clinical and roentgenologic data in these cases are similar, and in all of them the course of the disease was prolonged and the outcome favorable, except in my first case, in which the patient died of an intercurrent disease.

A point of special interest is the presence of pulmonary involvement in all of the Cuban cases and in my case 2. Since the patients in all 5 of these cases recovered, it has been impossible to ascertain the exact cause of the pulmonary shadows. However, the results of the histologic examinations of the bone marrow and the excised lymph nodes point to the possibility that the shadows were due to infiltration of the lung with eosinophilic cells. The observations on the liver in Atmar's case, previously referred to, are also suggestive in this connection.

The association of pronounced eosinophilia and pulmonary infiltration has been the subject of study by Löffler,[10] of Zurich; in 1931, and again in 1936, he called attention to this subject. He described a syndrome occurring in patients with tuberculosis which is characterized by the sudden appearance of extensive shadows in the pulmonary field which are transitory, sometimes lasting only a few days. The appearance of these shadows, which may resemble pneumonic infiltrations, is usually not accompanied by many physical signs or symptoms. In some cases the shadows were noticed during routine physical examinations. Coincident with the appearance of the shadows in the lung is a large increase in the number of eosinophilic cells in the circulating blood, in 1 case the proportion of eosinophils was 66 per cent. These symptoms are apparently transitory, and the patients are none the worse for them. The disease appears almost exclusively during the summer months (July and August). Since Löffler's original description of the condition was published, a great many cases have been reported.

That this syndrome is not confined to persons with tuberculosis is borne out by the fact that in 37 of Löffler's 51 cases the patient was given a tuberculin test and in 13 instances the reaction was negative.

I do not believe that the disease in my cases is related to that described by Löffler, for the following reasons: Pulmonary changes were present in only 1 of my 3 cases (case 2), and these pulmonary shadows remained for many months, while the lesions in Löffler's cases

10. Löffler, W.: Beitr. z. Klin. d. Tuberk. **79**:338, 1932; Schweiz. med. Wchnschr. **66**:1069 (Nov. 7) 1936.

were described as *flüchtige Lungeninfiltrate,* that is, transitory infiltrations. In the cases reported by Valledor and associates, the pulmonary changes were evident over a considerable period.

SUMMARY AND CONCLUSIONS

Three cases in which the disease was characterized by general adenopathy, leukocytosis and extreme eosinophilia and occurred in childhood have been reported.

In 1 the patient had roentgenographic evidence of miliary pulmonary infiltrations, which persisted for several years but finally disappeared.

The leukocytosis, and especially the eosinophilia, remained long after the fever had disappeared. The course of the disease is chronic but it may end in complete recovery.

In 1 case death occurred from intercurrent illness during the first year of observation. In the second case the patient was kept under observation for several years and finally recovered completely. In the third case, in which the patient is still being followed, there was a febrile period, but the child is now apparently in good health; the total leukocyte count has returned to normal, but a marked increase in eosinophilic cells still persists.

Data from 4 cases, reported from Habana, in which the disease resembled that in my cases are cited. The 7 cases resemble each other closely and appear to be examples of a clinical entity.

The relation of this syndrome to other pathologic states in which there are extreme leukocytosis and eosinophilia is discussed, and it is shown that the syndrome fails to fit into the category of any of the previously described conditions. Although the cause of the syndrome is unknown, it is most probably some type of chronic infection.

EMOTIONAL FACTOR IN BRONCHIAL ASTHMA IN CHILDREN

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Of recent date a great impetus is to be noted in the interest and attention devoted to the consideration of psychologic factors as related to disease and disease processes. One clinical condition which has received increased consideration from the psychogenic and the emotional point of view is bronchial asthma. McDermott and Cobb [1] reported the results of a psychiatric investigation carried out on 50 unselected patients with bronchial asthma in the allergy clinic of the Massachusetts General Hospital. They reported that the asthmatic condition of 37 of the 50 patients seemed to have emotional components. Careful inquiry into the previous history correlated the first asthmatic attack of 20 patients with some strongly emotional episode. The authors also found that subsequent attacks of asthma of 31 patients were precipitated by emotional upheavals.

Eyerman [2] expressed the opinion that "the time has come to study the emotional component of those with allergic disease . . ." He reported several cases of asthma in which the patients were materially benefited when a modification of the psychologic and emotional factors was undertaken.

It is unfortunate that a state of mutual suspicion and reluctance to accept each other's role in the study of allergic conditions so frequently exists between the pediatrician interested in allergy and the psychiatrist. Both should be concerned only with the lessons which can be learned through a cooperative, objective study of the conditions which have not responded to ordinary methods of diagnosis and treatment. It is common knowledge that some allergic manifestations are refractory to all forms of therapy. Likewise, there are times when exposure to the

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Read at the spring meeting of the Northwestern Pediatric Society, St. Paul, April 2, 1940.

From the Psychiatric Clinic for Children of the University Hospitals and the Department of Pediatrics of the University of Minnesota Medical School.

1. McDermott, N. T., and Cobb, S.: A Psychiatric Survey of Bronchial Asthma, Psychosom. Med. **1**:203, 1939.

2. Eyerman, C. H.: The Emotional Component of Bronchial Asthma, J. Allergy **9**:565, 1938.

sensitizing allergen does not precipitate an asthmatic attack. In addition, some patients with asthma tend to recover regardless of the type of therapy employed. Injections of physiologic solutions of sodium chloride have been too successful in curing some patients. What is the rationale, and who is there to explain it?

As one surveys the literature on the psychogenic and emotional factors in asthma, several facts of interest stand out. First, until recently much of the literature has come from foreign observers—notably German and English—and comparatively little from Americans; second, continuous reference is made in the literature to the importance of the early formative years of many of the patients studied, and, lastly, the results of few intensive psychiatric studies made on children with bronchial asthma have been reported. The most comprehensive work done to date of which we are aware is that reported on by Rogerson and his co-workers.[3]

We are reporting the cases of 4 children with refractory bronchial asthma who were referred to the psychiatric clinic for children of the University Hospitals for study and treatment. The presentation is of necessity detailed. Discussion of the points of interest revealed by these case studies and a brief report on some of the literature are offered.

REPORT OF CASES

CASE 1.—A., a 15 year old girl, had her first asthmatic attack at the age of 6 years. Previous to this she had had no allergic disease, and no other allergic manifestations were associated with the asthma. The mother had eczema, and the paternal grandfather had asthma. The child's tonsils and adenoids had been removed at the age of 4 years. The physical examination gave normal results. A roentgenogram showed some pulmonary emphysema. The laboratory examinations gave normal results, though the smears of material from the nose revealed many eosinophils and polymorphonuclear cells. The cutaneous tests for sensitivity gave consistently positive reactions to the cereal allergens and to house dust but no definite reactions to the pollens. The clinical impression was bronchial asthma. At times the attacks of asthma were accompanied by the secretion of much mucoid material and a productive cough. The results of the cutaneous tests were not encouraging for the instigation of any specific form of treatment.

Weekly or biweekly visits to the pediatric allergy clinic were common. The mother was overanxious and highly emotional. The patient was therefore referred to the psychiatric clinic for children since it was believed that she might be emotionally upset.

The family consisted of the father, the mother and the patient. The father, aged 53, a specialty salesman, of late years had been out of work and recently had worked on a project of the Works Progress Administration. As a salesman

3. (*a*) Rogerson, C. H.: Role of Psychotherapy in Treatment of Asthma, Eczema, Impetigo Complex in Children, Brit. J. Dermat. **46**:368, 1934. (*b*) Rogerson, C. H.; Hardcastle, D. H., and Duguid, K.: A Psychological Approach to the Problem of Asthma and the Eczema Prurigo Syndrome, Guy's Hosp. Rep. **85**:289, 1935.

he had been away from home much of the time. The impression was gained that no strong attachment existed between him and the family, as during interviews he was mentioned only casually by the mother and the patient. He was described as a quiet man, friendly and sociable in business matters but difficult to talk to and uncompanionable. These last traits had become more pronounced since his unemployment. The mother felt that he might be jealous of the intimate relationship that the patient and she enjoyed. The mother repeatedly blocked attempts to discuss relationship with her husband. The father never visited the psychiatric clinic.

The mother, aged 44, came from a good family in modest circumstances. Her childhood had been happy; strict standards of behavior were enforced, but severe punishment was seldom, if ever, used. While she was attending the university she had many friends, in particular a young man of whom she had been extremely fond. During that time, she had been much in the company of the patient's father, who, when he learned of her interest in the other man, "got busy" and soon married her. Before long she regretted her marriage. In interviews she was prone to idealize her former romance and to suggest that if her mother had been wise enough to encourage her friendship with the other suitor she would have married him instead.

The mother had been extremely lonesome during the early years of her married life until the birth of her daughter, around whom she had since centered most of her happiness; she was devoted to her child. She could never allow any one else to care for her and always played and talked with her a great deal. She deliberately kept the child dependent on her. Spontaneously during one of the interviews, the mother stated that she had "wished much of this illness on A." because it had increased the child's dependence. She had marked fears concerning the daughter, as was evidenced by the many precautions she had urged on her. Prior to the beginning of the psychiatric study the mother recognized that she and her daughter were beginning to drift apart. She feared this, dreading the day when her "daughter would grow away from her."

The patient was born nine years after the parents' marriage. She was neither wanted nor unwanted. Her development was average except for her health history. The mother always gave the patient "the best of care." Since the onset of the asthmatic attacks many physicians had been consulted, but little improvement had been noted. The mother expressed the belief that the patient had improved appreciably with treatment at the pediatric allergy clinic of the University Hospitals, although the attacks persisted.

The mother volunteered spontaneously that her daughter's dependence was the biggest problem. She felt responsible and guilty for this state of affairs. She stated that the patient expected to be waited on while she was sick.

The patient had made an excellent scholastic adjustment. Her interests were somewhat unusual in that she enjoyed classical literature and music. She had seldom participated in outdoor sports, but had often wanted to. Her friendships and activities had always been carefully selected and supervised by her mother.

A. was described as a pleasant youngster who was not sensitive or easily hurt and who presented no difficulty in management and readily accepted correction. In spite of being an only child she seemed to be unspoiled.

During psychiatric interviews the patient spontaneously recognized her dependence on her mother and, in addition, expressed resentment against the overanxiety and protectiveness displayed toward her. An intense source of conflict between the mother and the patient was the latter's choice of nursing as a professional career. The mother insisted that the patient could not engage in such

strenuous activity and favored training as an art teacher. Another source of irritation was the restriction imposed on the patient which prohibited participation in many of the usual activities of her contemporaries. She seldom went contrary to her mother's wishes, nor did she cry.

In interviews with the psychiatric social worker the mother was able to express some of the antagonism centering around her unhappy married life. The insight which she gained into the possible reasons for her attitude of anxiety and overprotectiveness toward the patient permitted the daughter more freedom. In addition, she was helped to discover new interests. In a comparatively short time the mother was able to accept the child's own decision for the future.

The patient responded to the diminishing domination of the mother. She was encouraged to attend a vocational high school to develop her artistic ability in anticipation of starting training in occupational therapy, a vocation which proved to be a compromise acceptable to the patient and to her mother. Early in the academic year the mother irritated the patient by repeated visits to the school but this practice was discouraged. The patient's social activities increased, as did her enjoyment of them. One morning during the time she was under psychiatric treatment an asthmatic attack developed before she left for school. However, instead of remaining at home to enjoy the attention bestowed on her by the mother as she previously had done, she took a capsule of ephedrine sulfate with amytal and left for school. It was a bitter struggle, but once she had got as far as the street car she felt much better and was able to remain in school the entire day. Shortly thereafter the patient improved so much that treatment was discontinued.

Nine months after the last contact with the patient she appeared at the clinic "for a visit." During the interview our suspicions concerning the relationship existing between the father and mother were confirmed when the patient informed us that her parents were separated. In discussing this change she readily acknowledged a feeling of relief from the emotional tension previously existing in the home. Her asthma had diminished and finally disappeared, and she no longer spoke of it.

Case 2.—B., a 16 year old girl, was first seen in the allergy clinic at the age of 15 years. She had had asthma for two years. The asthmatic attacks had not been preceded by any allergic disorder, nor had they been accompanied by any of the other common manifestations of allergy. The patient's maternal grandfather suffered from asthma, and one nephew had eczema. The condition of the chest as revealed by physical examinations was variable. During an attack coarse and sibilant rales were pronounced, but when the patient was free from asthma the chest was clear. The roentgenographic study showed bilateral maxillary and ethmoid sinusitis and some emphysema of both lungs. Differential blood counts at times gave a high percentage of eosinophils, and many eosinophils were present in smears of material from the nose. The cutaneous tests yielded positive reactions to animal danders and feathers. The patient was moved into an environment free of domestic animals, and feathers and danders were eliminated, but the results were not satisfactory. It was then discovered that prior to referral to the pediatric allergy clinic she had been under the supervision of no less than ten physicians and had not responded to any of the various forms of therapy attempted, including a four month change in residence. On one occasion she had had an attack so severe that she had lapsed into coma. For relief she had become dependent on frequent injections of epinephrine, often requiring as many as eight or ten during the twenty-four hours. The clinical impression was that her intractable asthma had a strong psychogenic component. She was therefore referred to the psychiatric clinic for children for study and further treatment.

At this clinic the following history concerning the family situation was elicited, primarily from the patient, but the statements were corroborated by interviews with the mother, the older sisters and the brother and by information received from the referring social agency.

The family consisted of the parents and 4 children, of whom B. was the youngest by five years. The father, regarded as a successful farmer until recent years, had become an excessive drinker, particularly during the past four years. He was said to be sober about two days of the week. When sober he was a mild-mannered person, but when intoxicated he neglected his responsibilities and was abusive and cruel to his wife and family. It was reported that he could not tolerate weakness in any one. He had always seemed to select the patient as a particular object for ridicule. Little is known about his early history.

The mother, a short, stocky, complacent woman, was described as hard working, conscientious and overprotective of and anxious about her children, especially the patient. She had left home several times because of her husband's alcoholism. Through her thrift and good management the family had been able to maintain control of the farm, which was heavily mortgaged. It was necessary for the family to accept relief on occasions.

Two older married sisters lived away from home but in the same neighborhood. The unmarried brother remained at home only when unemployed. The physical surroundings were moderately good, but the atmosphere of the home was described as one of extreme tension, anxiety and apprehension, due primarily to the father's drinking.

The patient was born three weeks prematurely. She had always complained of a "weak" stomach, but her developmental history was otherwise essentially normal. When 2 years of age she had a severe attack of convulsions of unexplained cause. As a small child she was extremely nervous and constantly shook her head, jerked her shoulders and pulled her hands. She had always fainted at the sight of blood. She was conscientious, liked other children and adults and never had presented disciplinary problems. She was described as having a pleasant personality and as being cooperative and helpful. However, she was inclined to be indecisive and averse to accepting responsibility. She had always slept with her mother.

The onset of asthmatic attacks seems to have coincided with the older brother's departure for employment in a neighboring state, which left the patient alone with the father and the mother. Whenever attacks of asthma occurred her father poked fun at her. Instead of securing medical aid he would scold her for not getting over them. In the midst of an attack he would harangue the patient by reading to her from a home remedy book. His alcoholism increased, as did his abusiveness. He would not return home until late at night. Because of the father's condition it was frequently necessary for the mother and daughter to do the chores. They would often retire and await his arrival in fear and terror, and on more than one occasion they had retired to the grove to escape his antagonism and belligerence. The father was a reckless smoker while drunk, and this created a fear that the house might be set on fire. On several occasions he had threatened to kill them. The mother, on the other hand, became more overprotective, upset and nervous.

When this family situation was discussed with an older sister her tension became so great that she broke down and wept bitterly. During our discussions the patient recounted many terrifying dreams and nightmares.

During the first few weeks following admission to the hospital B. was highly emotional and fearful and clutched desperately at any one who came into her

room. She became a nuisance to the nurses and physicians because of her dependent behavior. During an attack her breathing appeared to be extremely labored and signs of distress and anxiety were in evidence. It was repeatedly observed that the severity and duration of an attack were lessened if one talked to her quietly and encouragingly during its course.

Initially the patient was resistive to inquiry concerning personal worries or family conflicts. She was encouraged to discuss them frankly, but she remained adamant for several weeks. However, at the end of this time she suddenly began to express her feelings about the family situation more freely. A later interview with an older sister explained the sudden change in her attitude. It developed that she had written this sister requesting counsel as to whether or not she should discuss intimate family matters freely with us and had been encouraged to do so. She had seldom cried before this time, but as soon as she began to reveal conflicts centering around the hectic family situation she wept freely. At this point improvement in her asthma was noted. There was a distinct decrease in the severity and the number of attacks.

After this improvement she was placed in an open ward with other children, where she adjusted satisfactorily. After a month's hospitalization she was placed in a boarding home. She was encouraged to enter school and did reasonably well, when one considers that she had not attended school for over two years. After she was placed in the boarding home she remained almost free of symptoms for periods of as long as three months, requiring but one or two injections of epinephrine during that time. This was the longest that she had been able to do without the drug since she began to suffer from asthma.

The patient developed satisfactorily. She was no longer the clutching, fearful child previously described. Instead, she became poised and matter-of-fact and could discuss family antagonisms with surprising composure. She could express bitter resentment against her father without a sense of guilt. During the Easter holidays she returned home; it was her first visit in eight months. It was reported that the mother lay awake all during the first night, expecting her daughter to have an attack. However, the patient slept through the entire night with only one or two attacks of "hard breathing." Since that time there have been occasional recurrences, all of which centered around extreme emotional tension precipitated by contacts either with her mother or with her father.

CASE 3.—C., a 9 year old girl, was first seen in the allergy clinic after she had had attacks of bronchial asthma for four years. Although there had been no previous allergic disease, the patient now had allergic rhinitis in association with asthma. The mother had hay fever and had had eczema, and a maternal grandmother had hay fever and asthma. The physical examination showed that the child was somewhat poorly nourished. The tonsils and adenoids had been removed at the age of 5 years. The periodic roentgenographic studies revealed slight thickening of the mucous membrane of the maxillary sinuses and occasionally atelectsais. The laboratory examinations gave normal results, in spite of the fact that smears of material from the nose showed many eosinophils. The cutaneous tests gave positive reactions to a fairly large number of foods, to dog dander and to ragweed. The treatment was based on the elimination from the diet of the foods to which there were positive reactions, the removal of dogs from the child's environment and desensitization to ragweed. Progress was not consistent, and it was soon observed that the mother had an upsetting influence on the child. It was then that the patient was referred to the psychiatric clinic for children.

The family consisted of the father, the mother, an older sister, aged 14, and the patient. The father, a hard working man of good habits, provided reasonably well for his family. While he did not believe in disciplining the children he did occasionally roar at them, which upset the mother considerably. There seemed to be much subtle parental conflict. At times the father became overtly rebellious toward the mother because of her deep anxieties and concern.

The mother, a middle-aged, nervous woman, was under considerable tension and appeared chronically emotionally disturbed. Her background was good. After she had spent eighteen months in a school of nursing she became ill. The maternal grandmother persuaded the family physician to forbid the mother to return to the school; this she still resents. Interviews with the mother revealed subtle but real conflicts centering around marital maladjustments. The mother's instability was illustrated by her constant interference with the patient when she was placed in a temporary boarding home after discharge from the hospital. It was at this time that the patient had a massive collapse of the lung, after a severe emotional upheaval which took place when the mother interfered with the child's management in the temporary foster home. The mother had been described by previous attending physicians as "a pest."

The patient was born at full term. Her early development was average, although she was never robust. Whenever the patient was ill her mother had always been overprotective and solicitous, and this attitude had become more pronounced after the onset of the asthmatic attacks. These episodes were said to occur frequently and to keep the household in a constant turmoil. The patient, unable to attend school for several years, had been kept up to grade with the aid of the mother's tutoring. She was a charming, sophisticated youngster, who was initially distant and disdainful of recognizing others about her. She was stubborn and self sufficient but highly nervous.

While the patient was seen regularly in the psychiatric clinic, the major emphasis of treatment centered around a solution of the mother's problem. At first the mother was resistive during interviews, but she did continue them, with release of some of her tensions. This resulted in a temporary improvement in the family relationships, and C. immediately began to improve. Asthmatic attacks have occurred but rarely during the intervening four months. While the mother has continued to be concerned about the patient, her tension and anxiety have shown modification.

CASE 4.—D., a 10 year old girl, first began to have hay fever three years ago. This disease was followed by asthma. There have been no other allergic diseases. A paternal uncle had hay fever. The results of the physical and laboratory examinations were normal. The roentgenograms of the lungs showed no definite evidence of asthma. The mucous membrane of the paranasal sinuses showed considerable thickening. The cutaneous tests revealed many mild reactions to foods, inhalants and pollens. Hyposensitization therapy for the sensitivity to weed pollen was carried out, with some improvement. However, the patient continued to have asthmatic attacks after the pollen season, through the fall, winter and spring. The condition eventually became more difficult to treat by standard measures. It was at this time that the patient was thought to be considerably disturbed by the mother's interference. Because emotional factors appeared to play a contributing role, she was referred to the psychiatric clinic for children.

The family included the father, the mother, the patient and 2 younger siblings, aged 7 and 5 years. The father, who was in his thirties, was a mechanic who had been steadily employed. He was described as being an easy going, affable

man who enjoyed his occupation. He spent a good deal of the time away from home and apparently had not assumed much responsibility for the management of the family, although he was a good provider.

The mother, a highly nervous, erratic woman, was the oldest of 4 siblings. She was described as always having been determined, aggressive and extremely selfish. It was stated that she was unable to profit by suggestion or advice. She was opinionated and demanding. She had been inconsistent in her management of the child, and she could not forget that her daughter had asthma. She was particularly distressed and disagreeable when the father refused to accept a more remunerative job because he wished to continue living in his small community. During the past year the mother became fearful that the patient's younger brothers were becoming subject to asthma and took them repeatedly to physicians for examinations.

The patient was born after a long and difficult labor, during which forceps were used, with the production of marked injury to the head. She was cyanotic at birth, appeared listless and did not eat well. The forceps marks became infected and required lancing. Breast abscesses which required incision and drainage developed in the mother. Both the child and the mother were in the hospital for over a month after delivery.

The patient began developing well after a poor start, but she early displayed severe temper tantrums and would faint whenever her mother "pushed her too fast." At the age of 3 years she "passed out completely" after a tense emotional battle with the mother. At this time the patient began to have attacks of "hard breathing," which became so severe that when she was 5 or 6 years old she was taken to a physician, who said that she would outgrow the disorder. This did not occur. Instead, the patient's condition became progressively worse, with cyanosis accompanying some of her severe dyspneic spells. Lay friends advised the use of an epinephrine spray, which made the patient more nervous and excitable. However, she became markedly dependent on its use. More visits to other physicians did not lead to any improvement. She was then referred to the University Hospitals and was admitted in September 1939.

At this time she was losing weight and complained of contracting frequent colds. She began to complain also of "stomach ache." However, after one week of hospitalization she showed improvement and was discharged. In a special air-conditioned room at home she got along well until winter came. From Thanksgiving until Christmas time she was ill with colds, asthmatic attacks, abdominal pain, nausea and vomiting. In this connection it should be said that the patient had long been able to vomit any time she desired. This voluntary emesis began when she was 3½ years of age. It occurred frequently in retaliation against the mother.

The patient was an independent youngster. However, she was friendly and amenable to suggestion. There was a tendency to do the things which she liked and avoid those which she disliked. She was inclined to give up easily and to procrastinate with difficult tasks. This occurred particularly in projects involving the mother; with others she could be encouraged to proceed. She was alert and sensed quickly any changes in attitude or mood of the adults about her and reacted spontaneously to them.

Attendance at school had been erratic because of her physical upsets. However, she had maintained her grade by study at home.

Several weeks after the second admission to the University Hospitals she became free of symptoms and experienced no difficulty with her breathing. Whereas at home marked tension had developed because of her refusal to eat and to retire at a reasonable time, she fitted into the hospital routine without difficulty. She

retired at 9 p. m. and slept through the night. This was unusual, because at home she regularly awakened several times nightly and required the use of the epinephrine spray.

She was inclined to be careless about her personal appearance. Her hair was seldom combed and she enjoyed running around the ward in her pajamas, even though it was drafty and chilly at times. She was friendly with the other patients and for the most part cooperated well with the staff. However, there was a tendency to see how much she could "get away with."

After discharge from the hospital, she went to live with an aunt. She had no difficulty of note and regularly attended school, with satisfaction. She responded to consistent, firm discipline and entered into a good relationship with the rest of the family. She seldom wrote home. On one occasion she asked her aunt not to tell the mother that she was doing the dusting and washing the dishes there because then she would have to do them when she got home.

Comment on the Cases.—The patients in these 4 cases fall in the age range between 9 and 16 years, which means that they are quite comparable to the patients in the few studies previously reported on by others.[4] All have been girls. In a larger series a more equal distribution between boys and girls would undoubtedly be apparent.

Personality factors common to the group should be mentioned. All were highly nervous, under definite emotional tension and anxious. Cameron [5] and others [6] have referred to such tendencies as being characteristic of the asthmatic child. In patient A. these tendencies were particularly well controlled and were not manifest until after psychiatric investigation was begun. None of the 4 patients cried easily, which indicates repression. French [7] commented that most persons with asthma do not easily display emotion through weeping. This may be significant.

Several features common to the cases reported here should be mentioned. First, there is the multiplicity of sensitivities. In no case was there a single specific sensitivity. Second, in each case the disease was of long duration. In 3 cases the asthmatic attacks dated back to early childhood and were associated with a long history of bronchitis. In case 2 the patient was highly unstable and nervous prior to the onset of the asthmatic attacks. In each case there had been much discussion of the asthma before the child. Neighbors, relatives and school authorities in all cases entered the picture, with tremendous exaggeration of the differences between the patient and other children and stimulation of interest in and concern about the body. In each case an attitude of hopelessness concerning eventual recovery from the condition existed. This was the

4. (*a*) Strauss, E. B.: The Psychogenic Factor in Asthma, Guy's Hosp. Rep. **85**:309, 1935. (*b*) Rogerson.[3a] (*c*) Rogerson, Hardcastle and Duguid.[3b]

5. Cameron, H. C.: The Nervous Child, London, Hodder & Stoughton, 1919, pp. 165-166.

6. Strauss, E. B.: Psychogenic Asthma: A Record of Two Cases, Lancet **1**:962, 1927. Rogerson.[3a] Rogerson, Hardcastle and Duguid.[3b]

7. French, T. M.: Psychogenic Factors in Asthma, Am. J. Psychiat. **96**:87, 1939.

predominant attitude expressed either by the parents or by the patient, a state of mind not conducive to a favorable prognosis.

Cameron,[5] Rogerson [3a] and Strauss [4a] stressed the importance of the attitude of overprotectiveness and overconcern. Many cases have been reported in which a temporary cure occurred when the asthmatic child was removed from the tensions and anxieties of the home. Gillespie [8] emphasized the importance of psychologic factors in the evaluation of the problem of asthma. He likewise urged strongly that the entire situation be considered from the point of view of preventing the development of overanxiety and concern. Asthma creates a peculiar horror in the minds of many laymen.

It was stated that in C. a massive collapse of the lung developed immediately after an intense emotional situation created by the mother's active interference in a temporary foster home in which the child had been placed. The patient was at once admitted to the hospital for observation and care. No discernible causative factor could be elicited. We do not wish to suggest that intense emotion can produce a massive collapse of a lung. We mention the incident, however, as one in an interesting sequence of events.

The 4 cases presented for consideration illustrate the variations in mode of attack in the treatment of the psychologic factors in asthma. In case 1 both the mother and the child were given intensive therapy. In case 2 work with the patient was stressed. Most of the work was directed toward a release of her tensions and the development of insight into the role her emotional tensions played in the production of her many asthmatic attacks. In case 3 major attention was centered on the mother, although some work was done with the child. The patients in cases 1 and 3 remained in their own homes. Care in a boarding home was attempted in case 3, but it was unsuccessful. In order to eliminate the tensions created by the mother, the patient in case 4 was placed in the home of an aunt, where she did well.

COMMENT

Asthma is a disturbance of respiration in which two interrelated essential conditions manifest themselves: (1) A spasm of the bronchial musculature occurs in association with (2) excessive secretion of mucus, which is due in part to the swelling of the bronchial mucosal lining. Explanation of the bronchiospasm, as well as of the secretion and swelling of the bronchial mucous membrane, has heretofore been made largely in terms of allergy.

Some writers have expressed the opinion that the nervous factor in asthma has been recognized since antiquity and had been accepted unequivocally until the recent intensive advances were made in the study

8. Gillespie, R. D.: Psychological Factors in Asthma, Brit. M. J. **1**:1289, 1936.

of allergic reactions during the past twenty years. Eyerman [2] reviewed the changes in concept, using Osler's "Principles and Practice of Medicine" as an example. This classic textbook on medicine was first published in 1892. In the first edition bronchial asthma was described as primarily a "neurotic affliction." It was not until the twelfth edition, in 1935, that the word "neurosis" was deleted. However, in this edition, under "etiology," a section on "psychic causes" occurs, in which it is stated that anxiety neurosis and emotional states are important in asthma. Garrod, Batton, Thursfield and Paterson [9] suggested that asthma may be thought of as one of the manifestations of an unstable nervous system.

The process of respiration is now recognized to be under the control of the respiratory center, located in the region of the fourth ventricle. This center is bilateral, each portion being located laterally from the midline at the level of the calamus scriptorius.

The extrinsic and intrinsic nerves of the respiratory tract are the vagus and the autonomic fibers. An intimate relation of these nerves with the respiratory center, as well as with other basal nuclei, exists. Kuntz [10] expressed the belief that intense emotional states may cause definite bronchiospasms as well as mucosal changes. He suggested further that asthmatic conditions may result from disturbances in pulmonary innervation.

Jelliffe and White [11] and Garrod and his associates [9] suggested that asthmatic attacks may be precipitated by one of three channels: (1) reflexly through the nervous system, (2) by chemical substances or changes in the blood stream which influence the respiratory center directly and (3) by psychologic disturbances.

A modification of the illustration of Langden and Brown suggested by Brown [12] represents this concept diagrammatically:

Psychic Stimuli
↓
Peripheral Stimuli→Respiratory Nucleus←Foreign Protein
↓
Bronchomotor Spasm←Vagus Nuclei→Vasomotor Turgescence

While the exact mode of production of bronchial asthma is not known, it may be one or more of the mechanisms mentioned. That peripheral stimulation acting reflexly and chemical changes acting

9. Garrod, A. E.; Batton, F. E.; Thursfield, H., and Paterson, D.: Diseases of Children, ed. 2, New York, William Wood & Company, 1929, p. 349.

10. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929, p. 179.

11. Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System, ed. 6, Philadelphia, Lea & Febiger, 1935, p. 199.

12. Brown, W. L.: Problems of Asthma, Proc. Roy. Soc. Med. (Sect. Therap. & Pharm.) **16**:1, 1923.

directly on the respiratory center induce changes in the respiratory tract via the vagus seems reasonable. It is only through recent research that the third possible mode of action, through psychic stimulation in the nature of emotional tensions, seems to be nearing clarification.

The influence which intense, acute emotional reactions have on the respiratory functions of the body is well recognized. Catching of the breath during fright, heavy labored breathing during intense anger and the like are common examples. These are usually transitory, representing only momentary changes. However, explanation of the influence of protracted worry, fears and anxieties has been more difficult until recently. Grinker,[13] in a classic review of the relations and functions of the hypothalamus, which is claiming so much attention at the moment, suggested the importance of this structure as a center which controls and directs the discharge of emotional tension. It may be that adequate explanation of the emotional factors will be made when there is a more thorough understanding of this little known and important area.

Ingvar [14] expressed the opinion that nervous people, being sensitive to the import of environmental influences, also possess a lowered threshold for allergic reactions. He further suggested that biologic changes occur in the neurons of the respiratory apparatus after the first asthmatic attack, which provides a reaction pattern which later may be set in motion by purely psychogenic factors.

We concur in the belief expressed by Gillespie [8] that psychic factors in and of themselves cannot and do not cause asthma but that such factors can be, and often are, significant in the disease.

SUMMARY AND CONCLUSION

On the basis of our own observations and those reported by others, we should like to emphasize the importance of recognizing and dealing with emotional factors in every case of asthma, but more particularly in those cases in which the disease is refractory to the usual therapy.

The early recognition of psychologic factors seems advisable if the possibility of a subsequent condition of semi-invalidism is to be prevented. It is ordinarily the rule to consider psychogenic and emotional factors only when everything else has failed. A more logical procedure would be to take cognizance of their importance and to make a conscious effort to deal with them early in the case of each individual patient suffering from bronchial asthma.

This form of cooperative enterprise will be continued, and further observations will be reported in future communications.

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13. Grinker, R.: Hypothalamic Functions in Psychosomatic Interrelations, Psychosom. Med. **1**:19, 1939.

14. Ingvar, I.: The Physical Basis for Psychoneurosis, Lancet **1**:343, 1936.

RELATION OF STREPTOCOCCIC ANTIFIBRINOLYSIN TO ACUTE RHEUMATIC FEVER

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Since the frequent association of infection with the beta hemolytic streptococcus and acute rheumatic fever has been generally recognized, the possible etiologic significance of this organism has been extensively studied. No attempt will be made in this paper to summarize the entire literature, but certain contributions that have a direct bearing on the present study will be cited.

In 1932 Todd [1] and Coburn [2] studied the antistreptolysin titer in the serum of the same group of patients with rheumatic disease. This antibody inhibits the ability of the beta hemolytic streptococcus to hemolyze the red cells of the rabbit in vitro, and its concentration in blood serum can be readily measured by a standard dilution technic. The authors noted that in practically all cases of acute rheumatic infection there was a definite increase in the titer of this antibody and suggested that the results support the theory, advanced by Coburn,[3] that the hemolytic streptococcus is a causative agent of rheumatic disease. Their results have been confirmed by other workers (Myers and Keefer,[4] McEwen and his co-workers,[5] Coburn and Pauli [6] and Longcope [7]).

From the Departments of Pediatrics and Bacteriology, University of Rochester School of Medicine and Dentistry, and Strong Memorial and Rochester Municipal Hospitals.

1. Todd, E. W.: Antihaemolysin Titres in Haemolytic Streptococcal Infections and Their Significance in Rheumatic Fever, Brit. J. Exper. Path. **13**:248, 1932.

2. Coburn, A. F., and Pauli, R. H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process: III. Observations on the Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus, J. Exper. Med. **56**:651, 1932.

3. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931.

4. Myers, W. K., and Keefer, C. S.: Antistreptolysin Content of the Blood Serum in Rheumatic Fever and Rheumatoid Arthritis, J. Clin. Investigation **13**: 155, 1934.

5. McEwen, C.; Bunim, J. J., and Alexander, R. C.: Bacteriologic and Immunologic Studies in Arthritis: II. Results of Various Immunological Tests in Different Forms of Arthritis, J. Lab. & Clin. Med. **21**:465, 1935.

(Footnotes continued on next page)

In 1933 Tillett and Garner [8] found that certain strains of the beta hemolytic streptococcus produced a substance capable of liquefying human fibrin and demonstrated the presence in human serum of a specific antibody, which was termed antifibrinolysin, in contrast to the antistreptolysin of Todd. The titer of antifibrinolysin is measured by the time required for an effective strain of the beta hemolytic streptococcus to produce complete lysis of the subject's plasma clot. (The clot of a normal person is completely lysed in from twenty to sixty minutes, while that of a patient convalescing from an infection with beta hemolytic streptococcus may resist lysis for twenty-four hours or more. The blood

TABLE 1.—*Reported Titers of Antifibrinolysin in Cases of Acute Rheumatic Fever*

Author	Number of Cases	Antifibrinolysin Titer		
		Low	Intermediate	High
Hadfield, G.; Magee, V., and Perry, C. B.: The Lysis of Fibrin by Streptococci, Lancet **1**: 834, 1934	9	4	1	4
McEwen and co-workers [5]	35	4	12	19
Meyers, W. K.; Keefer, C. S., and Holmes, W. F., Jr.: The Resistance to Fibrinolytic Activity of the Hemolytic Streptococcus, with Special Reference to Patients with Rheumatic Fever and Rheumatoid (Atrophic) Arthritis, J. Clin. Investigation **14**: 119, 1935	20	2	5	13
Harris, C. H. S.: A Study of Hemolytic Streptococcal Fibrinolysis in Chronic Arthritis, Rheumatic Fever, and Scarlet Fever, Lancet **2**: 1456, 1935	8	4	3	1
Tillett [9]	8	0	5	3
Waaler, E.: Development of Antifibrinolytic Properties in the Blood of Patients with Rheumatic Fever, Chronic Infectious Arthritis, and Bacterial Endocarditis, J. Clin. Investigation **16**: 145, 1937	7	1	1	5
Perry [10]	44	11	33	
Boisvert, P. L.: Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**: 65, 1940	33	3	..	30

serum of such a patient would be considered to have a high content of antifibrinolysin).

Studies of antifibrinolysin in cases of rheumatic disease have been made by numerous investigators (table 1), who have found that the majority of patients with an acute process show a definite increase of

6. Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process, I. The Determination of Antistreptolysin Titer, J. Exper. Med. **62**:129, 1935.

7. Longcope, W. T.: Studies of the Variations in the Antistreptolysin Titer of the Blood Serum from Patients with Hemorrhagic Nephritis: II. Observations on Patients Suffering from Streptococcal Infections, Rheumatic Fever, and Acute and Chronic Hemorrhagic Nephritis, J. Clin. Investigation **15**:277, 1936.

8. Tillett, W. S., and Garner, R. L.: The Fibrinolytic Activity of Hemolytic Streptococci, J. Exper. Med. **58**:485, 1933.

antifibrinolysin by the time clinical symptoms develop. The incidence of increased amounts of antibody in this group agrees closely with that in groups of nonrheumatic persons convalescing from infections with beta hemolytic streptococci (Tillett [9]) and strongly supports the concept that most attacks of rheumatic fever are at least preceded by infections with this organism.

The report of Perry [10] deserves comment because it deals with a large series of cases and concerns the relation of antifibrinolysin to acute rheumatism. In 11 (25 per cent) of his 44 cases there were typical attacks of acute rheumatic fever without any increase of the antibody under consideration, though in 1 case a high titer developed during a subsequent attack. Perry reached this conclusion: "There is no correlation between the duration of antifibrinolysin and the duration of the rheumatic attack or between antifibrinolysin and the severity of the rheumatic attack."

During the past three years the significance of the antifibrinolysin titers of an unselected group of children with rheumatic fever and rheumatic heart disease has been under investigation. The present report, however, deals only with studies on those children for whom a definite clinical diagnosis of acute rheumatic fever was established. Most of the antifibrinolysin titers were determined during the active phase of the disease.

METHOD

The method used for the routine determination of the antifibrinolysin titer was similar to that described by Tillett and Garner [8] in 1933. It was found that Douglas' [11] broth served as a satisfactory medium for the production of fibrinolysin. The strains of beta hemolytic streptococci employed were obtained from patients with streptococcic infections, and selection was made solely on the basis of fibrinolytic activity. A strain was discarded when this activity became weak. Often more than one strain was used for a test, but in no case did the simultaneous use of several strains give rise to conflicting results. The streptococci were carried in serial subcultures of Douglas' broth, with transfer to a tube of the broth containing a drop of rabbit's blood once a week. With this technic it was possible to maintain strains in an active condition for several months or longer.

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9. Tillett, W. S.: The Occurrence of Antifibrinolytic Properties in the Blood of Patients with Acute Hemolytic Streptococcus Infections, J. Clin. Investigation **14**:*276*, 1935.

10. Perry, C. B.: The Relationship Between Acute Rheumatism and Streptococcal Antifibrinolysin, Arch. Dis. Childhood **14**:*32*, 1939.

11. Douglas, S. R.: On a Method of Making Cultivation Media Without Prepared Peptones, and on a Peptone-Free Medium for Growing Tubercle Bacilli, Lancet **2**:891, 1914.

The samples of oxalated plasma (a 0.2 per cent solution of potassium oxalate was used) were prepared from blood obtained directly from the patient's vein or from blood previously drawn for the determination of the sedimentation rate. Tests were always made during the first twenty-four hours after the blood was obtained. By the simultaneous testing of several patients it was possible to provide a normal control (plasma of a patient with no increase in antifibrinolysin) in each series. This served as a check on the fibrinolytic ability of the organisms used for each test.

Because the work of Massell, Mote and Jones[12] has cast some doubt on the accuracy with which the antifibrinolysin titer can be measured by the time required for the complete lysis of a clot, the following broad groupings have been used for the interpretation and arrangement of the results:

1. If the clot was not completely lysed in twenty-four hours the titer of antifibrinolysin was considered high.

2. If the clot was completely lysed in from three to twenty-four hours the titer of antifibrinolysin was considered intermediate.

3. If the clot was completely lysed in less than three hours the titer of antifibrinolysin was considered low.

This classification is similar to Perry's.

RESULTS

The present study is based on one hundred and seventy tests performed on the plasma of 73 children who had clinical evidence of acute rheumatic fever. Most of them were patients in bed in the pediatric service of the Strong Memorial or the Rochester Municipal Hospital at some time between the summers of 1937 and 1940. The children were tested two or more times during each attack of the disease except in a few instances in which the period of hospitalization was so short that only one test was made.

In an effort to evaluate the significance of the antifibrinolysin titer, the patients were arranged in three groups, according to the titer of the antibody. Group 1 was composed of 46 patients with a high titer of antifibrinolysin (resistance of the clot to lysis for at least twenty-four hours), 4 of whom had a second rheumatic attack during the period of observation. For 42 the titer was high early in the course of the disease (35 were tested during the first week of hospitalization) and remained so until the clinical signs of activity had subsided. The second of a series of tests on 1 patient showed a low titer, while all of the others were high. This single irregular result might be interpreted as being due to an error. For 3 patients the first test indicated an intermediate titer, while all of the subsequent samples showed a high titer. It should be emphasized that in none of the fifty attacks suffered by these 46 patients did the antibody titer change from low to high during the

12. Massell, B. F.; Mote, J. R., and Jones, T. D.: The Quantitative Relation of Fibrinolysin and Antifibrinolysin, J. Immunol. **36**:45, 1939.

course of the acute disease, although the reverse was true during convalescence.

Group 2 was composed of 7 patients with an intermediate titer of antifibrinolysin. For 4 who were tested on more than one occasion the

TABLE 2.—*Clinical Data for Patients with Acute Rheumatic Disease Grouped on the Basis of Their Streptococcic Antifibrinolysin Titers*

	Group 1 (High Titer)	Group 2 (Intermediate Titer)	Group 3 (Low Titer)
Age	4-14 years (average, 10)	6-11 years	3-16 years (average, 9.9)
Sex	27 boys, 19 girls	5 boys, 2 girls	10 boys, 10 girls
Percentage incidence* of:			
Arthritis	(40/51) 78†	(6/7) 86	(14/22) 64
Chorea	(6/46) 11	(1/7) 14	(3/20) 15
Heart block	(25/47) 53†	(4/7) 59	(11/17) 65
Pericarditis	(5/51) 10†	(1/7) 14	(4/22) 18
Decompensation	(6/51) 11†	(0/7) ..	(5/22) 23
Pericarditis or decompensation ‡	(8/51) 16†	(1/7) 14	(7/22) 32
Duration of activity:			
Less than 4 weeks	(11/40) 28	(2/6) 33	(2/17) 12
4-6 weeks	(16/40) 40	(1/6) 17	(12/17) 71
More than 6 weeks	(13/40) 33	(3/6) 50	(3/17) 18
Preceding infection of upper respiratory tract	(30/46) 65	(4/8) 50	(10/22) 45
Previous attack	(13/50) 26	(1/7) 14	(6/22) 27
Tonsils present	(21/44) 48	(4/7) 59	(10/20) 50
History of rheumatic disease in other member of family	(8/46) 17	(3/7) 43	(6/26) 30
Negative reaction to Dick test	(21/45) 64	(5/7) 71	(12/17) 71
Culture of material from throat:			
Beta hemolytic streptococci present	(10/44) 23	(3/7) 43	(9/22) 41
Beta hemolytic streptococci predominant	(5/44) 11	(1/7) 14	(2/22) 9
Season attack occurred:			
Spring	29	4	11
Summer	6	2	..
Fall	3	..	7
Winter	2	1	4
Years attacks occurred: §			
1936-1937	4	0	1
1937-1938	14	3	11
1938-1939	9	2	4
1939-1940	23	2	6

* The figures in parentheses preceding the percentage figure indicate the number of times the clinical feature occurred in the number of attacks observed.

† Including the 1 patient whose titers put him in group 2 during the first attack observed and in group 1 during the second.

‡ Calculation of the percentage incidence of this feature on the basis of the number of patients who had the symptoms instead of the number of attacks showed: group 1, 17 † per cent (8/47); group 2, 14 † per cent (1/7), and group 3, 35 † per cent (7/20)

§ Data for 1936-1937 are incomplete. The number of patients listed for 1936-1937 represent 20 per cent of the patients with rheumatic fever admitted in that year, for 1937-1938 39 per cent, for 1938-1939 27 per cent and for 1939-1940 19 per cent.

titer remained constant during the period of clinical activity of the disease. One patient suffered a recrudescence of rheumatic activity during the following year, and this illness was characterized by a high titer.

Group 3 was composed of 20 patients who had a low titer of antifibrinolysin during the acute rheumatic attack. Fourteen of them were

tested on two or more occasions throughout the period of clinical activity. Furthermore, 2 patients had second attacks, and the same low titer persisted.

The constancy of the antifibrinolysin titer for each patient suggested that a comparison of data for the three groups might throw some light on the significance of this antibody in acute rheumatic fever. In table 2 the data are arranged so as to permit ready comparison. Because the group which is intermediate with respect to antibody titer contained only 7 patients, it does not merit as much emphasis as the other two.

A brief comment on some of the data used for comparison is desirable. Groups 1 and 3 show the same age distribution. There is a slight predominance of boys in group 1. The incidence of arthritis is appreciably higher in this group than in group 3. While there were but few attacks of chorea in any group, the incidence is uniform. The diagnosis of heart block was made when the PR (Q) interval in the electrocardiogram exceeded the normal value for the age and the heart rate as given by Ashman and Hull.[13] This condition was present during about two thirds of the attacks of the patients in group 3 and in one half of the attacks of those in group 1. Pericarditis and cardiac decompensation appear almost twice as frequently in group 3 as in group 1. Because the incidence of each of these symptoms was low, the incidence of the two combined was calculated, but the same ratio between the incidence in the groups persisted, and calculating the percentages on the basis of the number of patients who had the symptoms instead of the number of attacks did not change it.

The duration of activity was estimated by repeated determinations of the sedimentation rate. The disease was not considered inactive until the rate had returned to normal. According to this standard, there is little difference between the groups. In group 3 the duration of activity for almost three quarters of the attacks was from four to six weeks. There was much more variation in group 1.

A history of preceding infection of the upper respiratory tract was more frequent in group 1. The incidence of previous rheumatic disease was the same for groups 1 and 3. The percentage of tonsillectomized children was about the same in each group. The history of rheumatic disease in other members of the family was more frequent in group 3, but too much reliance cannot be placed on this factor because of the way in which routine histories vary.

The percentage of children with a negative reaction to the Dick test is approximately the same in all groups. Contrary to what might be

13. Ashman, R., and Hull, E.: Essentials of Electrocardiography, New York, The Macmillan Company, 1937.

anticipated, beta hemolytic streptococci were found more frequently in cultures of material from the throat for group 3 than in those for group 1. If one considers only those cultures in which this organism predominated, the incidence is equal. More than one culture of material from the throat was made for only a few of the patients, and no special methods were adopted to isolate the hemolytic streptococci. This may account for the low total number of cultures positive for these organisms. The distribution of attacks according to seasons and years is approximately the same for all groups. The figures for 1936-1937 are not reliable, because so few patients were studied.

In these studies no evidence was obtained to suggest that there is more than one type of fibrinolytic substance produced by the various strains of beta hemolytic streptococci, an observation which is in agreement with the results of previous work (Tillett [14]).

COMMENT

It would appear that 1 of every 4 patients with typical acute rheumatic fever has no appreciable increase of antifibrinolysin in the serum. The incidence of 28 per cent (of 73 cases) obtained in the present study is in close agreement with that of 25 per cent (of 44 similar cases) reported by Perry,[10] and the correlation is strengthened by the fact that widely different groups of children were tested with varied strains of the beta hemolytic streptococcus.

The proponents of the theory of a streptococcic causation of rheumatic fever will immediately point out, as Perry has done, that the antifibrinolysin titer of the same percentage of nonrheumatic persons convalescing from known beta hemolytic streptoccic infections fails to increase. Therefore, it is conceivable that such an infection precedes every attack of acute rheumatism and that in 25 per cent of the cases the titer fails to rise above the normal level.

To support or refute the role of the hemolytic streptococcus in the causation of rheumatic fever is not the purpose of the present study, which was planned to throw light on the significance of the antifibrinolysin titer in this disease. Does a high titer of this antibody constitute an asset or a liability to the patient during the rheumatic attack? A partial answer to this question may be obtained from a consideration of the comparison made in table 2. On the basis of these data, the hypothesis might be sustained that a patient with rheumatic fever who has a low antibody titer is less apt to have involvement of joints, but is more apt to have first degree heart block and is twice as likely to have pericarditis or cardiac decompensation. The differences

14. Tillett, W. S.: The Fibrinolytic Activity of Hemolytic Streptococci, Bact. Rev. **2**:161, 1938.

between groups 1 and 3 are not statistically significant, but the results all point toward the same conclusion, namely, that a high titer of antifibrinolysin may be associated with some protective mechanism against cardiac involvement in cases of acute rheumatic fever.

The foregoing conclusion is not in agreement with Perry's statement that "the appearance of resistance to streptococcal fibrinolysin in the blood of patients with acute rheumatism is not an essential part of the rheumatic process." Unfortunately, he presented only 6 cases in detail, but in 2 of them pericarditis was associated either with a low or with a rapidly decreasing titer of antibody. Apparently, the titer of several patients in his series fluctuated considerably during the acute attack. This is in contrast to the observations made in the present study. Perry and Waaler each reported a case with fatal termination in which the antibody titer was high. There were no deaths among the patients studied in the present series.

Indirect evidence in support of the hypothesis previously advanced is obtained from the results of Lippard and Johnson [15] and McIntosh and Wood.[16] The former workers noted that most children under 3 years of age apparently lack the capacity to develop antifibrinolysin after hemolytic streptococcic infections. The latter investigators have reported that rheumatic fever occurs in the same age group more commonly than is generally appreciated but that it is characterized by a high incidence of carditis and a relatively low incidence of arthritis.

The lack of a constant correlation between the titers of antifibrinolysin and and antistreptolysin has been demonstrated by Harris [17] and by Lippard and Johnson. However, a comparison of the titers of these two antibodies for a large series of patients with rheumatic fever has not been reported. In his early studies of antistreptolysin, Todd [1] reported that the titer was elevated in 22 of 23 cases of rheumatic fever. It is interesting to note that in the single case in which there was a low titer of this antibody pericarditis without arthritis was present.

No attempts were made to explain why the antibody response of all of the patients was not more uniform on the basis of the results of the present study. Three hypotheses might be suggested: (1) In not all cases of rheumatic disease is there a previous beta hemolytic strepto-

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15. Lippard, V. W., and Johnson, P.: Beta-Hemolytic Streptococcic Infection in Infancy and Childhood: I. Antifibrinolysin and Antistreptolysin Response, Am. J. Dis. Child. **49**:1411 (June) 1935.

16. McIntosh, R., and Wood, C. L.: Rheumatic Infections Occurring in the First Three Years of Life, Am. J. Dis. Child. **49**:835 (April) 1935.

17. Harris, C. H. S.: Hemolytic Streptococcal Fbrinolysis, Brit. J. Exper. Path. **16**:513, 1935.

coccic infection; (2) some constitutional defect which prevents adequate antibody formation is present in 1 patient of every 4 and (3) not all virulent beta hemolytic streptococci possess the same fibrinolytic ability. This last hypothesis is supported by experimental work (Tillett).[14]

SUMMARY

An unselected series of 73 children with acute rheumatic fever has been studied for the amount of streptococcic antifibrinolysin present in the blood. Twenty-eight per cent of the patients had typical rheumatic fever, without an appreciable increase in antifibrinolysin during the active stage of the disease. It was found that the patients could be readily separated into three distinct groups on the basis of antibody titer: high, intermediate and low. Correlation of the antifibrinolysin titer with various clinical features of the acute rheumatic attacks provided no explanation for the marked differences in titer.

A comparison of the data for the groups with high and low titers suggests that a patient with acute rheumatic fever who has a low titer of antifibrinolysin may be less apt to have arthritis but may be more apt to have heart block, pericarditis and cardiac decompensation. The data are not statistically significant; nevertheless, it may be that in the acute stage of rheumatic disease a high titer of this antibody is associated with some mechanism which tends to prevent cardiac involvement.

FOLLICULAR CONJUNCTIVITIS IN SCHOOL CHILDREN AS AN EXPRESSION OF VITAMIN A DEFICIENCY

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For a number of years one of us (L. J. G.), in his capacity as county health officer, has observed a high incidence of follicular conjunctivitis among the white school children whom he has examined.

This condition has been noted in various sections of the country. Williams,[1] in a study of 4,000 school children from the east side of New York city, found many with the disorder. She stated that it occurs primarily among children of elementary school age and is practically unknown among children more than 16 years old. Williams suggested a relation between the occurrence of such trachoma-like conditions and "a lack of proper nourishment and an abnormal amount of sweet stuffs" in the diets of the children affected. A few years later Jervey[2] discussed the prevalence of conjunctival folliculosis in South Carolina and stated that whenever large numbers of children are examined the condition will be found in a considerable number of them, without regard to the economic or the educational status. He urged caution in the treatment of children for trachoma and expressed the belief that many persons with conjunctival folliculosis have been subjected unnecessarily to the drastic treatment customarily given those with trachoma.

From the Florida State College for Women and the Leon County Health Unit.

White Laboratories, Inc., Newark, N. J., furnished the capsules of cod liver oil concentrate which were used for the experiment with the children in series 2.

The data included in this report are taken from theses submitted by Helen Dorothy Cate, in May 1938, and Kathleen Perry Wilkinson, in May 1939, to the Faculty of the Florida State College for Women in partial fulfilment of the requirements for the degree of Master of Science.

1. Williams, A. W.: A Study of Trachoma and Allied Conditions in the Public School Children of New York City, J. Infect. Dis. **14**:261, 1914.

2. Jervey, J. W.: The Differential Diagnosis of Conjunctival Folliculosis and Trachoma, J. A. M. A. **75**:1112 (Oct. 23) 1920.

At the time Jervey's article was published and for some years later there was considerable difference of opinion with regard to the differentiation of follicular conjunctivitis from trachoma. Williams [1] cited Boldt as authority for the statement that many of the earlier estimates of the prevalence of trachoma are unreliable because of the inclusion of allied conditions, such as follicular conjunctivitis, under the general classification of trachoma. McMullen [3] recognized the distinction between trachoma and allied conditions but advocated that all doubtful disorders be treated as trachoma. Thygeson [4] stated that in the European literature American ophthalmologists were frequently said to be unable to draw a clear distinction between the two diseases. Howard,[5] in 1933, still considered the "unitarian" theory of follicular conjunctivitis as an attenuated form of trachoma sufficiently important to warrant discussion, although he expressed the opinion that an overwhelming majority of ophthalmologists subscribed to the "dualistic," or "pluralistic," theory.

Jervey [2] described the childhood disease as "characterized by a varying degree of adenoid hypertrophy of the subepithelial lymphoid elements of the conjunctiva . . . invariably tending, after a longer or shorter period to spontaneous and complete recovery." Stucky [6] suggested the use of the term "adenomatous conjunctiva" rather than follicular conjunctivitis or conjunctival folliculosis, as it emphasized the hypertrophy of the adenoid tissues of the subepithelial layer and made unnecessary the differentiation of the form of the disease with inflammation from that without. Julianelle [7] based his differentiation of follicular conjunctivitis from trachoma primarily on the absence of inclusion bodies in the former disease. He called attention to the distribution of the follicles in more or less parallel rows in follicular conjunctivitis, stating that the lower lid is more often involved than the upper and that the folliculosis never invades the cornea or forms scar tissue.

The relation of dietary deficiency to follicular diseases of the eye has been studied in connection with trachoma. Royer [8] suggested that

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3. McMullen, J.: A Public Health Problem of the States, J. A. M. A. **75**:1109 (Oct. 23) 1920.

4. Thygeson, P.: Biomicroscopy of the Limbus Corneae in Trachoma and Other Conjunctival Diseases, Am. J. Ophth. **17**:787 (Sept.) 1934.

5. Howard, H. J.: The Diagnosis of Trachoma, Am. J. Ophth. **16**:132 (Feb.) 1933.

6. Stucky, J. A.: Trachoma: Suggestions as to Diagnosis, Etiology and Treatment, South. M. J. **19**:140 (Jan.) 1926.

7. Julianelle, L. A.: The Etiology of Trachoma, New York, The Commonwealth Fund, Division of Publications, 1938.

8. Royer, F.: Need of Epidemiological Research in Trachoma, Am. J. Pub. Health **16**:706 (July) 1926.

there is need for a reevaluation of all evidence and "a broadgage epidermiological research into every possible influence that might permit trachoma to develop, whether it is due primarily to a food fault or to a specific virus." Stucky [6] prescribed cod liver oil and a liberal diet for patients with trachoma and stated that the use of these measures in conjunction with the usual medical and surgical procedures eliminated recurrences of the disease. Rice, Sory, Smith, Faed and Drake,[9] on the other hand, found no evidence of improvement when cod liver oil and a balanced diet were given to patients under their supervision. Tilden and Miller [10] inoculated normal and vitamin A–deficient monkeys with Bacterium granulosis but were unable to produce follicular lesions in either group of animals. Hetler and James,[11] in an intensive study of the influence of diet on the transmissibility of trachoma to monkeys, found that, if anything, there was a decrease in the severity and a lengthening of the incubation time of the disease in monkeys fed a diet deficient in vitamin A as compared with controls receiving adequate supplies of vitamin A.

Ocular lesions resulting from a deficiency of vitamin A were described in 1923 by Yudkin and Lambert.[12] They studied microscopically the tissues of young rats which had early, moderate and late stages of deficiency. They showed that increased lacrimation was observed consistently during the early stages of deficiency and that the earliest lesions "consist in focal inflammatory lesions in the conjunctivae of the lids and nictitating membrane. The involvement of the cornea, which constitutes the most conspicuous feature of the well developed ophthalmia, is a secondary phenomenon." Shortly after, Wolbach and Howe [13] showed that the substitution of keratinizing epithelium for normal epithelium constituted the fundamental tissue change in vitamin A deficiency, and attention seems to have been diverted from the observation of Yudkin and Lambert that involvement of the palpebral conjunctiva precedes involvement of the cornea. In line with the early report, however, is

9. Rice, C. E.; Sory, R.; Smith, J. E.; Faed, P. E., and Drake, A. A.: The Effect of Diet and Vitamins on Trachoma, Am. J. Ophth. **17**:735 (Aug.) 1934.

10. Tilden, E. B., and Miller, E. G.: Response of Monkeys to the Withdrawal of Vitamin A from Diet, J. Nutrition **3**:121 (Sept.) 1930.

11. Hetler, R. A., and James, W. M.: The Influence of Dietary Deficiency on the Transmissibility of Trachoma to Monkeys, Am. J. Ophth. **17**:1048 (Nov.) 1934.

12. Yudkin, A. M., and Lambert, R. A.: Pathogenesis of the Ocular Lesions Produced by a Deficiency of Vitamin A, J. Exper. Med. **38**:17 (July) 1923.

13. Wolbach, S. B., and Howe, P. R.: Tissue Changes After Vitamin A Deficiency, J. Exper. Med. **42**:753 (Dec.) 1925.

a recent comment by Yudkin [14] on the clinical improvement of patients with phlyctenular conjunctivitis following vitamin A therapy.

INCIDENCE OF FOLLICULAR CONJUNCTIVITIS AMONG SCHOOL CHILDREN OF LEON COUNTY, FLA.

In the fall of 1938 the eyes of 1,041 school children enrolled in grades 1 to 9, inclusive, were examined for evidences of follicular conjunctivitis. The opportunity was afforded by the routine medical examination made of all the white school children of Leon County by one of us (L. J. G.). We believe that the children examined are representative of the county as a whole.

From table 1, which presents the results of this survey by school grade, it is seen that the 32.8 per cent incidence of follicular conjunc-

TABLE 1.—*Incidence of Conjunctival Folliculosis Among Children Enrolled in Grades One to Nine*

Grade	Children Enrolled	Children with Conjunctival Folliculosis	
		Number	Percentage
1	134	44	32.8
2	106	28	26.4
3	129	34	26.4
4	134	36	28.9
5	119	25	21.0
6	121	22	18.2
7	125	18	14.4
8	115	14	12.2
9	58	5	8.6
Total	1,041	226	21.7

tivitis in the first grade declined gradually to an 8.6 per cent incidence in the ninth, with an average of 21.7 per cent. More than 100 children were examined in each of the first eight grades. The number examined in the ninth grade is smaller, and the data secured are therefore a less reliable measure of the incidence among children of this grade level. Under the conditions of the examination some instances of mild forms of the disease may have escaped detection; so the incidence reported must be considered minimum rather than maximum. The statistical treatment of these data in table 2 indicates that the difference between the incidence in grades 1 and 2 and that in higher grades does not become significant until the seventh and eighth grades are reached, though it approaches significance in the sixth and seventh.

In view of the prevalence of follicular conjunctivitis among the school children of this section of Florida, it has seemed important to us to study it in relation to the nutritional status of the children affected.

14. Yudkin, A. M.: Vitamins in Treatment and Prevention of Ocular Diseases, Arch. Ophth. **19**:366 (March) 1938.

EXPERIMENTAL OBSERVATIONS

Series 1.—During the fall of 1937, one year prior to the study on the incidence of follicular conjunctivitis already mentioned, 39 children with a moderately severe form of the disease were selected for study. They were enrolled in one elementary school and were examined and selected by one of us (L. J. G.) in the course of the annual examination of the white school children in the county.

A survey of the diets of these children (discussed in detail in a later section of this paper) indicated a shortage of vitamin A. On the basis of this observation, a supplementary midmorning lunch, which included a rich source of vitamin A, was given to 22 of the children selected for study. Seventeen children, closely matched with regard to age and the severity of the conjunctival folliculosis, constituted a control

TABLE 2.—*Difference in the Incidence of Conjunctival Folliculosis Among Children in Grades One and Two and Among Those in Higher Grades*

Grades	Children Enrolled	Children with Conjunctival Folliculosis		Actual Difference in Percentage Incidence of Conjunctival Folliculosis in Grades 1 and 2 and in Succeeding Grade Groups *	Difference in Percentage Incidence
		Number	Percentage		Standard Error of the Difference
1 and 2	240	72	30.0 ± 2.0	.....	...
3 and 4	263	70	26.6 ± 1.8	3.4 ± 4.0	0.8
5 and 6	240	47	19.6 ± 1.7	10.4 ± 3.9	2.7
6 and 7	246	40	16.3 ± 1.6	13.7 ± 3.7	3.7
7 and 8	240	32	13.3 ± 1.5	16.7 ± 3.7	4.5

* The standard errors were computed according to formulas 104, 105, 106 and 107, respectively, from Holzinger (Statistical Methods for Students in Education, Boston, Ginn & Company, 1928, pp. 248-250).

group and received no dietary addition. The supplementary feeding was begun Feb. 14, 1938 and was continued until April 14.

Five times weekly the children in the experimental group received approximately 25,600 U. S. P. units of vitamin A in the form of a concentrate of fish liver oil. In addition, one-half pint (237 cc.) of milk containing approximately 711 U. S. P. units of vitamin A was given to each child daily, since a large number of the children in both the experimental and the control group were receiving free milk from one of the civic organizations. This complicated the situation from the standpoint of the experiment but appeared to be unavoidable, and the milk did facilitate the ingestion of the capsules. All supplements were taken under the immediate supervision of one of us (H. D. C.).

Two weeks after the supplementary feeding was begun, the children were reexamined (by L. J. G.) to confirm the diagnosis made during the fall examination. It was obvious that improvement had occurred in a number of cases, and it seemed important to record more systematically the observed severity of the conjunctival folliculosis and of

such related conditions as the injection and edema of the eyelids and the watery discharge from the eyes. In conjunction with these ocular symptoms there was frequently a distinct dryness of the skin, similar to that which was observed by Sweet and K'ang,[15] Frazier and Hu[16] and more recently, Lehman and Rapaport.[17] This dryness was noticeable when the upper part of the arm or the thigh was examined.

Systematic checking of the foregoing symptoms in both the experimental and the control group was carried out March 3. Six weeks later, on April 7, both groups were examined again, and on April 14 a final examination of all the children was made.

TABLE 3.—*Symptoms of Vitamin A Deficiency Shown by Children in Control and Experimental Groups After Two, Eight and Nine Weeks of Supplementary Feeding* *

		Follicles on the Conjunctiva					Injection of the Eyelids			Edema of the Eyelids			Crusting of the Eyelids			Dryness of the Skin		
	Time After Beginning Supplementary Feeding, Weeks	No. Showing Symptom	No. Improved	Percentage Improved	No. Free	Percentage Free	No. Showing Symptom	No. Improved	Percentage Improved	No. Showing Symptom	No. Improved	Percentage Improved	No. Showing Symptom	No. Improved	Percentage Improved	No. Showing Symptom	No. Improved	Percentage Improved
Experimental group (22 children)	2 (March 3)	22	0	0	0	0	22	0	0	16	0	0	12	0	0	17	0	0
	8 (April 7)	13	20	91	9	41	9	13	59	4	12	75	2	10	83	1	16	94
	9 (April 14)	11	21	95	11	50	†	†	†	†	†	†	†	†	†	†	†	†
Control group (17 children)	2 (March 3)	17	0	0	0	0	17	0	0	12	0	0	15	0	0	10	0	0
	8 (April 7)	17	0	0	0	0	17	0	0	12	0	0	15	0	0	10	0	0
	9 (April 14)	17	0	0	0	0	†	†	†	†	†	†	†	†	†	†	†	†

* The supplementary feeding was begun Feb. 14, 1938.
† Examinations with regard to this symptom were not made.

Results: Table 3 gives data for the children in the control and experimental groups with regard to the symptoms of deficiency shown on examination two, eight and nine weeks after the supplementary feeding was begun. In no instance had there been improvement in any symptoms of the children in the control group. Of the children who received supplementary feeding, 9, or 41 per cent, had entirely clear conjunctivas by April 7, and 11, or 50 per cent, were entirely free of symptoms by April 14. All but 1 of the remainder showed a

15. Sweet, L. K., and K'ang, H. J.: Clinical and Anatomic Study of Avitaminosis A Among the Chinese, Am. J. Dis. Child. **50**:699 (Sept.) 1935.

16. Frazier, C. H., and Hu, C. H.: Cutaneous Lesions Associated with a Deficiency in Vitamin A in Man, Arch. Int. Med. **48**:507 (Sept.) 1931.

17. Lehman, E., and Rapaport, H. G.: Cutaneous Manifestations of Vitamin A Deficiency in Children, J. A. M. A. **114**:386 (Feb. 3) 1940.

decrease in the size and the number of follicles. This 1 subject had reacted positively to a test for the presence of hookworms in the fall but had refused treatment. Apparently, a heavy infection with hookworms had precluded any beneficial effect from the ingestion of the vitamin concentrate.

The related symptoms showed striking improvement. The dry skin was gradually replaced by skin having a normal amount of oil and moisture, and the dried secretion on the cheeks and eyelids became less obvious, indicating distinct lessening of the discharge. The injection and edema improved more slowly, decreasing in severity at about the same speed as the conjunctival folliculosis improved.

Series 2.—Because of the encouraging results with the children in series 1, a second study of greater scope was planned for the early part of 1939.

Eighty elementary school children with follicular conjunctivitis of varying degrees of severity were selected (by L. J. G.) as suitable subjects for study. They were divided into four groups, matched as evenly as possible with regard to age, severity of symptoms and economic status. Those in group 1 received no supplement; those in group 2 received a concentrate containing approximately 13,000 U. S. P. units of vitamin A and a negligible amount of vitamin D per dose; those in group 3 received a cod liver oil concentrate which provided about 25,000 U. S. P. units of vitamin A and 2,500 U. S. P. units of vitamin D per dose, and those in group 4 received both the cod liver oil concentrate and the concentrate of stabilized vitamin A esters, so that each dose contained approximately 38,000 U. S. P. units of vitamin A. All of the children in groups 2, 3 and 4 received with their vitamin supplement a small cup of a punch containing synthetic fruit acid, coloring matter and sugar, which helped them to swallow the supplements and created a "party" atmosphere which they enjoyed. This supplementary feeding was given under the personal supervision of one of us (K. P. W.) during the midmorning lunch period of the school.

The experiment ran from Jan. 4 through April 3, 1939, and all children in both the experimental and the control group were examined (by L. J. G.) at intervals of approximately three weeks. The score used in evaluating the severity of the conjunctival folliculosis is given in table 4. The accompanying figure shows typical examples of follicular conjunctivitis.

Results: The course of the disease in the members of the control and of the experimental group is indicated in table 5. Forty, or 66.67 per cent, of the 60 children given supplementary feedings were entirely free of follicular conjunctivitis before the end of the twelve week experimental period, and all of the remaining 20 showed improvement. In general, children who had 1 plus or 2 plus conjunctival folliculosis at

TABLE 4.—*Score Used in Evaluating the Severity of the Follicular Conjunctivitis at the Beginning of the Experiment and After Healing of the Lesions Had Begun*

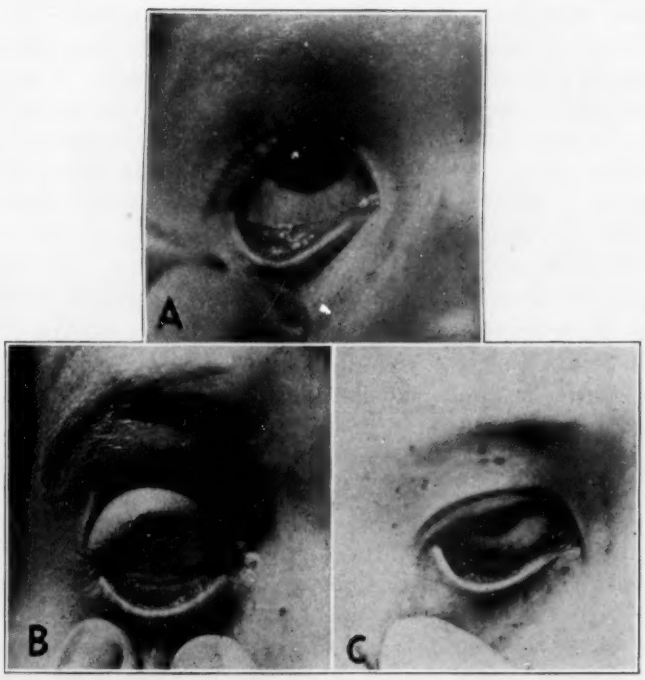
At Beginning of Experiment		During Healing of Lesions	
Score	Criteria	Criteria	Score
		Follicles extend across lower lid and into corner of upper lid	++++
+	Follicles on lateral corner of conjunctiva protruding like pinpoints	Definite rounding off of follicles present and decrease in size of some	+++
++	Follicles extend half across lower lid	Considerable decrease in size of follicles and disappearance of some of the smaller ones	++
+++	Follicles 2 to 3 mm. in diameter extend across lower lid	Disappearance of a considerable number of follicles and reduction in size of those left	+
++++	Follicles 2 to 3 mm. in diameter extend across lower lid and into corner of upper lid		

TABLE 5.—*Course of Follicular Conjunctivitis in Treated and Untreated Children over the Twelve Week Experimental Period**

		Children Given No Supplementary Vitamin A			Children Given 13,000 U.S.P. Units of Vitamin A 5 Times Weekly			Children Given 25,000 U.S.P. Units of Vitamin A 5 Times Weekly			Children Given 38,000 U.S.P. Units of Vitamin A 5 Times Weekly			All Children Given Supplementary Vitamin A		
Original Severity of Disease	Date of Medical Examination	Total	No. Improved	No. Recovered	Total	No. Improved	No. Recovered	Total	No. Improved	No. Recovered	Total	No. Improved	No. Recovered	Total	No. Improved	No. Recovered
+	January 4.....	9	..	..	8	..	..	11	..	..	4	..	..			
	January 27.....		0	0		0	0		1	1		0	0			
	February 24.....		0	0		3			3	3		2	2			
	March 20.....		..	..		7	7		11	11		4	4			
	April 3.....		0	0		8	8		11	11		4	4	23	23	23
++	January 4.....	6	..	..	9	..	..	4	..	..	3	..	..			
	January 27.....		0	0		2	0		2	0		1	0			
	February 24.....		0	0		5	0		3	0		1	0			
	March 20.....		..	..		7	6‡		4	4		1	1			
	April 3.....		1†	0		9	6		4	4		3	2	16	16	12
+++	January 4.....	5	..	..	5	..	..	4	..	..	3	..	..			
	January 27.....		0	0		1	0		0	0		2	0			
	February 24.....		1†	0		4	0		3	0		3	1			
	March 20.....		..	0		4	1		4	0		3	1			
	April 3.....		1†	0		5	3		4	0		3	2	12	12	5
++++	January 4.....	..	..	..	4	..	..	4	..	..	1	..	..			
	January 27.....		..	..		3	0		1	0		0	0			
	February 24.....		..	..		3	0		2	0		1	0			
	March 20.....		..	..		3	0		3	0		1	0			
	April 3.....		..	..		4	0		4	0		1§	0	9	9	0

* The experimental period began Jan. 4, 1939.
† Received lunch provided by the Parents and Teachers Association.
‡ Unfavorable reaction to diphtheria toxoid.
§ Had an excessive number of absences from school.

the beginning of the period improved more rapidly than did those with the more severe forms of the disease. By the end of the experimental period all of the children in groups 2, 3 and 4 who had 1 plus conjunctival folliculosis at the beginning of the experiment were entirely clear of the condition; of the 16 who had a 2 plus grade of the disease at the beginning of the experiment, 12 were entirely free of the condition and the remaining 4 were improved. Of the 12 with 3 plus conjunctival folliculosis at the beginning of the experiment, 5 were entirely free of the disease and all of the remainder were improved. Of the 9



Typical examples of follicular conjunctivitis (series 2). *A*, photograph of C9, taken Jan. 23, 1939, during the early weeks of the experiment; the conjunctival folliculosis was graded 2 plus. *B*, photograph of C11, taken Jan. 30, 1939, showing 4 plus conjunctival folliculosis and dried secretion on the margins of the eyelids. *C*, photograph of B20, taken Jan. 23, 1939, showing severe (4 plus) conjunctival folliculosis.

children who had a 4 plus grade of the disease at the beginning of the experiment, none were free of the folliculosis at the end of the experiment but all showed improvement.

In the group receiving no supplement, 2 children who had 2 plus and 3 plus conjunctival folliculosis, respectively, at the beginning of the experiment showed slight improvement before the end of the period. Inquiry

disclosed that, unknown to us, these children had received each school day a free lunch provided by the local parents and teachers association. This, lunch, which consisted of a large bowl of vegetable soup made of carrots, tomatoes and turnip greens, plus a slice of bread and a half pint (237 cc.) of milk, had a vitamin A content of approximately 600 U. S. P. units.

In all three of the groups which received supplements of vitamin A, healing of the lesions appeared to proceed at approximately the same rate, although the children in group 3 received twice as much of the vitamin and those in group 4 three times as much as those in group 2. Apparently there is a time element which limits the speed of the healing process, and excessive amounts of vitamin A do not increase the rate of healing in proportion to the size of the supplements.

It has been shown by Sherman and Cammack [18] with young rats, by Rowntree [19] with children and by Riggs [20] with cattle that there is a definite limit to the amount of vitamin A which can be stored in the growing organism. In harmony with these observations is the case of 1 child, C9, whose ocular condition during the early weeks of the experiment is shown in *A* of the figure. He was free of conjunctival folliculosis when examined on April 3, and unsuccessful efforts were made to secure a picture of the normal conjunctiva on April 17 and April 24. On May 8, when a third effort was made to get a picture of the conjunctiva, it was found that the folliculosis had returned. This child had received five times weekly over a period of twelve weeks 38,000 U. S. P. units of vitamin A. Five weeks after the supplement was discontinued, beginning signs of conjunctival folliculosis indicated that the reserves of vitamin A provided earlier were exhausted and that the child was again in a condition of deficiency.

Vitamin A was supplied in these experiments from two different sources, one a concentrate of cod liver oil which provided both vitamin A and vitamin D and the other a concentrate of stabilized vitamin A esters which contained a negligible amount of vitamin D. Since both were effective in improving the symptoms of follicular conjunctivitis, vitamin D as a factor in the improvement was ruled out. Feeding the children in series 2 a synthetic beverage in place of the milk given those in series 1 did not alter the response to the supplements, which shows that constituents in the milk other than its vitamin A content made no important contribution to the improvement noted in the children of series 1.

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18. Sherman, H. C., and Cammack, M. L.: A Quantitative Study of the Storage of Vitamin A, J. Biol. Chem. **68**:69 (April) 1926.

19. Rowntree, J. I.: A Study of the Absorption and Retention of Vitamin A in Young Children, J. Nutrition **3**:265 (Nov.) 1930.

20. Riggs, J. A.: The Length of Time Required for Depletion of Vitamin A Reserves in Range Cattle, J. Nutrition **20**:491 (Nov.) 1940.

Some of the children improved more rapidly than did others who had lesions of approximately the same degree of severity and received the same supplements. In a few cases the delay in healing appeared to be related to the presence of other physical disorders. One child (C11) had improved steadily during the first nine weeks of the experimental period, at the end of which time he was given diphtheria toxoid and had fever for several days. Examination showed that the original severity of the discharge from the eyes returned and that no further improvement in the folliculosis occurred during the remaining weeks of the experiment. In a second child (B18) mild jaundice developed. Although she was absent from school only a few days, her eyes improved more slowly than did those of others of her group. This is of interest in view of the work of Greaves and Schmidt,[21] who observed in rats a relation between jaundice and failure to utilize carotene. The case of a third child seems worthy of note. B20, who was heavily infected with hookworms, showed no improvement during the first eight weeks of the study. Eight days after the usual treatments for hookworm infection were given, the score for his follicular conjunctivitis had dropped from 4 plus to 2 plus. He continued to improve, though his eyes were not entirely normal when he was last seen. The case of this child, like that of the child in series 1 previously mentioned, emphasizes the unfavorable influence of hookworm infection on the utilization of vitamin A.

DIETARY SURVEY

In connection with these studies we have analyzed the diets of 58 elementary school children.

During January 1938 a record of the diet during one week was secured from each of 15 families, which included among their members 18 children with follicular conjunctivitis. During October, November and December of 1938 similar records were collected from 35 families. Among the members of 20 of these were 25 children with follicular conjunctivitis; 14 families had 15 children entirely free of such symptoms, while 1 family had 1 child with and 1 without follicular conjunctivitis. Both the normal and the deficient group included children from families which were on relief or were receiving work relief through the Works Progress Administration, from families of industrial and office workers and from families of well-to-do professional men.

Cooperation of the mother or guardian was secured in each case through a personal visit to the home, and the dietary record was started under the supervision and with the assistance of one of us (K. P. W.

21. Greaves, J. D., and Schmidt, C. L. A.: The Utilization of Carotene by Jaundiced and Phosphorus Treated Vitamin A Deficient Rats, Am. J. Physiol. **111**:502 (April) 1935.

or H. D. C.). An inventory of the food on hand was taken at the beginning and at the end of the seven day period, and a daily record was kept of the food bought or otherwise secured. The family menus were recorded each day, and a careful check was made of the child's food intake and of any foods which he did not eat or which were served to him exclusively. Analysis of these combined records and a discussion of them with the mothers enabled us, we believe, to secure a reasonably accurate estimate of the vitamin A content [22] of the diet ingested by each child.

Table 6 gives the total vitamin A content of the diet per day and the vitamin A content per kilogram of body weight per day for each child. Of the children with well developed follicular conjunctivitis, 14 received less than 50 U. S. P. units of vitamin A per kilogram per day and 17 received between 50 and 99 units, while only 3 of the normal group of children received less than 100 U. S. P. units of vitamin A per kilogram per day. Ten children with and 5 children without follicular conjunctivitis received between 100 and 158 U. S. P. units of vitamin A per kilogram of body weight per day. Vitamin A values of 160 U. S. P. units and over per kilogram of body weight per day apparently give protection from the deficiency. The 1 child not protected by a diet apparently high in vitamin A belonged to a family on relief which was eating at that particular time a diet consisting almost exclusively of sweet potatoes, which had just been harvested.

A large proportion of the vitamin A content of these diets was derived from the carotene present in the fruits and vegetables ingested, though the more liberal diets contained somewhat more preformed vitamin A in the milk, cream, butter and eggs used. It appears that diets of this character which supply less than 100 U. S. P. units of vitamin A per kilogram of body weight per day will allow symptoms of deficiency to develop in practically all cases. Diets which supply 100 to 160 U. S. P. units of vitamin A per kilogram of body weight per day will protect many, but not all, children. Diets which supply vitamin A in excess of this amount may be considered to furnish protection, though not necessarily to allow for storage, if the children are able to utilize the vitamin ingested. In view of these observations an average mixed diet which supplies 200 to 250 U. S. P. units of vitamin A (ingested both as carotene and as preformed vitamin A) per kilogram of body weight per day seems a conservative tentative standard for children of elementary school age.

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22. Rose, M. S.: A Laboratory Handbook of Dietetics, ed. 4, New York, The Macmillan Company, 1937. Biologic units have been converted into international units by using the factor 0.75, as recommended by the Council on Foods of the American Medical Association in its recent publication (Accepted Foods, Chicago, American Medical Association, 1939, p. 8).

TABLE 6.—*Vitamin A Content* of the Diets of Children from Representative Families of Leon County, Fla.*

Child	Children with Conjunctival Folliculosis				Children Free from Conjunctival Folliculosis		
	Score for Folliculosis	Weight, Kg.	Vitamin A Content of Diet, U. S. P. Units	Vitamin A Content per Kg. of Body Weight, U. S. P. Units	Weight, Kg.	Vitamin A Content of Diet, U. S. P. Units	Vitamin A Content per Kg. of Body Weight, U. S. P. Units
W. P.	++++	34	302	9			
N. B.	++++	34	769	23			
A22	+++	29	686	24			
A9	++	32	810	25			
R. L.	++	34	990	29			
P. B.	++	31	953	31			
B. G.	++	25	865	35			
F. M.	++	38	1,463	39			
M. L.	+++	25	990	40			
D9	.....	..	.....	..	39	1,580	41
A17	++	25	1,079	43			
B10	+	32	1,478	46			
B1	+	33	1,569	47			
M. A.	+	31	1,455	47			
R. D.	++	31	1,444	47			
G. F.	+++	29	1,470	51			
C10	+++	21	1,103	52			
C. S.	++	38	2,051	54			
C1	+	26	1,500	58			
C7	++	21	1,230	59			
B22	++++	23	1,425	62			
R. T.	+++	31	1,937	63			
A25	++++	22	1,457	66			
H. M.	++++	22	1,463	67			
A11	++	18	1,230	68			
A3	+	39	2,702	69			
R. G.	++	22	1,553	71			
J. M.	+++	20	1,463	73			
B. M.	+++	29	2,253	78			
B11	+	35	2,919	83			
M. K.	++	25	2,258	90			
D4	.....	..	.....	..	29	2,663	92
C6	++	37	3,440	93			
D1	.....	..	.....	..	31	3,078	99
B12	++	26	2,705	100			
D8	.....	..	.....	...	32	3,249	102
A2	+	19	1,989	104			
A6	+	23	2,609	113			
D6	.....	..	.....	...	28	3,182	114
B15	++	35	4,287	122			
P. L.	+++	20	2,520	125			
D3	.....	..	.....	...	33	4,317	131
D2	.....	..	.....	...	24	3,171	132
A7	+	21	2,814	134			
D13	.....	..	.....	...	28	3,980	142
B6	+	26	3,735	143			
A12	++	20	2,975	149			
A13	++	20	3,143	157			
B5	+	22	3,470	158			
D12	.....	..	.....	...	35	5,853	167
D10	.....	..	.....	...	26	4,068	187
D11	.....	..	.....	...	25	5,324	213
D7	.....	..	.....	...	22	4,811	219
D15	.....	..	.....	...	30	6,771	225
A23	++++	24	5,885	245			
D14	.....	..	.....	...	19	4,712	248
D16	.....	..	.....	...	29	8,447	291
D5	.....	..	.....	...	28	9,977	356

* The term vitamin A content refers both to preformed vitamin A and to carotene, in accordance with the definition of vitamin A approved by the Council on Foods of the American Medical Association (Accepted Foods, Chicago, American Medical Association, 1939, p. 7).

SUMMARY

One hundred and nineteen children with follicular conjunctivitis of varying degrees of severity were studied with regard to the effect of supplementary vitamin A on the folliculosis.

Twenty-one of the 22 children in series 1 who received supplementary vitamin A showed improvement, and of these 11 were entirely free of follicular conjunctivitis at the end of the nine week experimental period. No improvement occurred in the eyes of any of the 17 children in the control group observed over the same period.

All of the 60 children in series 2 who received graduated amounts of vitamin A were improved, and 40 were entirely free of follicular conjunctivitis by the end of the twelve week experimental period. Of 20 children who received no supplementary vitamin during this same period, none except 2 who had received a more liberal diet showed any improvement.

Children who received 13,000 U. S. P. units of vitamin A improved at approximately the same rate as did those who received 25,000 or 38,000 U. S. P. units. Apparently a time factor operates which limits the rate of healing of the lesions, and excessive doses of vitamin A do not increase this rate proportionately.

A concentrate of vitamin A esters which contained a negligible amount of vitamin D produced as rapid improvement in the follicular conjunctivitis as did a concentrate containing vitamin D. One-half pint of milk given to the children in series 1 in addition to the vitamin concentrate gave no better results than were secured with vitamin A alone. Deficiency of vitamin A appears to be the specific factor concerned in the development of follicular conjunctivitis in school children.

A survey of the diets of 58 children, of whom 42 had follicular conjunctivitis and 16 did not, indicates that in practically every instance consumption of a diet which had a vitamin A content below 100 U. S. P. units per kilogram of body weight per day allowed the deficiency to develop. Diets of which the vitamin A content was between 100 and 160 U. S. P. units per kilogram of body weight protected some, but by no means the majority, of the children who consumed them. Diets with a vitamin A content in excess of this amount appear to protect children of the ages studied from follicular conjunctivitis. It is suggested that in diets in which carotene furnishes a large proportion of the vitamin A value 200 to 250 U. S. P. units of vitamin A per kilogram of body weight per day will provide a none too generous allowance for children between the ages of 6 and 12 years.

Our data indicate that the presence or absence of follicular conjunctivitis as an indication of the state of vitamin A nutrition is a more reliable measure for children 6 to 12 years of age than for older boys and girls.

NONSPECIFIC ULCERATIVE COLITIS IN CHILDHOOD

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Nonspecific ulcerative colitis is characterized by the appearance of bloody diarrhea, resulting from inflammatory changes in the large bowel, which can be ascribed to no definite cause. That this condition occurs in childhood is not generally appreciated, and the reports in the literature and textbooks are reticent on this subject. In 1909 Allchin [1] stated: "I have never seen in children postmortem the appearance of the ulcerations in the large intestines in any way resembling that which is constant in the disease in adults." Morse [2] did not mention any cases of ulcerative colitis in his review of 14,000 cases of recurrent abdominal pain in children. Helmholz,[3] in 1923, reported the first 5 recorded cases of ulcerative colitis in children. There followed reports by Bourine [4] in 1926, Helmholz [5] in 1926 and again in 1936, Wagner [6] in 1928, Greenbaum [7] in 1929, Lamson [8] in 1931, Winkelstein [9] in 1931 and Jackman and associates [10] in 1940.

From the Pediatric Service of Dr. Béla Schick, Mount Sinai Hospital.

1. Allchin, W. H.: Ulcerative Colitis, Proc. Roy. Soc. Med. (Med. Sect.) **2**:59, 1908-1909.

2. Morse, J. L.: Recurrent Attacks of Abdominal Pain, J. Pediat. **4**:725 (June) 1934.

3. Helmholz, H. F.: Chronic Ulcerative Colitis in Childhood, Am. J. Dis. Child. **26**:418 (Nov.) 1923.

4. Bourine, G.: Chronic Ulcerative Colitis in Children, Arch. Dis. Childhood **1**:175 (Jan.) 1926.

5. Helmholz, H. F.: Chronic Ulcerative Colitis in Childhood, New York State J. Med. **26**:46 (Jan. 15) 1926; Chronic Ulcerative Colitis in Childhood, Ohio State M. J. **32**:941 (Oct. 1) 1936.

6. Wagner, W. P.: A Case of Ulcerative Colitis in a Child, Canad. M. A. J. **18**:571 (May) 1928.

7. Greenbaum, L. H.: Ulcerative Colitis in Children, Arch. Pediat. **46**:584 (Sept.) 1929.

8. Lamson, O. F.: Chronic Idiopathic Colitis in Children, S. Clin. North America **11**:1065 (Oct.) 1931.

9. Winkelstein, A.: Nature and Treatment of Non-Specific Ulcerative Colitis, New York State J. Med. **31**:1400 (Nov. 15) 1931.

10. Jackman, R. J.; Bargen, J. A., and Helmholz, H. F.: Life Histories of Ninety-Five Children with Chronic Ulcerative Colitis, Am. J. Dis. Child. **59**:459 (March) 1940.

From 1927 to the present 23 patients with the disease have been observed in the wards of the Mount Sinai Hospital. The patients ranged in age upward from 2 weeks, with no definite predominance of any age group. Fifteen were boys and 8 girls. The race and the nationality of the parents appeared to have no definite influence on the predisposition to the disease. Seasonal variations were not associated either with the onset or with the recurrence of the disorder.

CLINICAL, PATHOLOGIC AND ETIOLOGIC CHARACTER OF NONSPECIFIC ULCERATIVE COLITIS

Onset.—The acuteness of the disease at onset varies, and the severity of the course differs from time to time and from patient to patient. In this series infants had the more severe forms of the disease. The following brief case report is illustrative.

A. R., a 5 month old white girl of Italian parentage, was admitted to the hospital on Feb. 8, 1933 with a history of watery diarrhea associated with the passage of blood and mucus, which had begun twenty-four hours before. One month before the present admission she had been treated for pneumonia, and at that time her stools were considered normal. Examination showed that the child was moderately well developed. There were several pustular lesions over the buttocks, thighs and rectum. The remainder of the examination gave essentially normal results. During her stay in the hospital the stools contained frankly bloody, purulent material. Proctoscopic examination on three occasions revealed marked ulcerations of the rectal mucosa, and ulcerative colitis was suspected. Despite supportive measures, the child's course was progressively downhill, and she died forty-eight days after admission.

Laboratory studies revealed negative reactions to the Wassermann and Mantoux tests, persistent neutrophilic leukocytosis and red cell counts varying from 4,800,000 to 4,300,000. Cultures of material from the stools and the ulcers contained the usual enteric organisms. Necropsy showed areas of hyperplasia of the Peyer patches in the jejunum and the ileum. In the terminal portion of the ileum there were numerous small ulcerations, but in the large intestine there were large ulcerations, with purulent exudate. Cultures of material from the ulcers contained Bacillus coli.

The disease may also manifest itself as chronic relapsing colitis. The following brief case report is illustrative.

B. S., a 10 year old Jewish boy, was admitted to the hospital on Feb. 15, 1939. Eighteen months previous to admission the mother had noted that the child began to lose his appetite and to become fatigued easily. The weight dropped steadily. A few months later there appeared symptoms referable to the gastrointestinal tract, which consisted of cramplike abdominal pain associated with three to four watery stools a day. He began to have a low grade fever and red blood in his stools. Between this time and the date of admission he was treated in two other hospitals with little success.

Examination revealed a poorly developed, chronically ill child. There were no external signs specific for the disease. The reaction to Wassermann and

Mantoux tests were negative. Sigmoidoscopic examination showed an edematous thickened mucosa with several irregular ulcerations which were covered with a grayish membrane. The cultures of material from the ulcerations and from the stools failed to yield organisms other than the usual intestinal flora. The patient remained in the hospital for thirteen weeks and slowly improved with the consumption of a high calory, high vitamin, low residue diet. At the time of discharge sigmoidoscopic examination showed that considerable healing had occurred.

On July 17, at the age of 11 years, the boy was readmitted, because of an exacerbation which was characterized by the passage of eight to ten watery stools a day and low grade fever. Aside from pallor, his physical status was as observed on the previous admission. Sigmoidoscopic examination revealed a granular mucosa, which appeared to be healing. Various therapeutic measures, such as parenteral administration of liver extract, feeding of a high vitamin diet and transfusions, were tried, but no improvement was noted. After a course of anti-colon-bacillus serum the child began to show signs of improvement. The fever disappeared, and his appetite increased. The number of liquid stools was reduced to two per day. He was discharged as improved after a stay of three months in the hospital. However, on November 3, sixteen days later, he was readmitted, for the same complaints. Again on sigmoidoscopic examination the sigmoid mucosa appeared granular, and the cultures were negative for specific pathogenic micro-organisms. The treatment consisted of administration of azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate), daily enemas of cod liver oil and intramuscular injections of liver extract. Improvement began, and he was discharged on December 6, after arrangements had been made for further observation and treatment in the outpatient department.

At the last follow-up examination, six months later, this child's disease was still in an active stage. He appeared ill, had low grade fever and had lost 3 pounds (1.3 Kg.)) in one month. The hemoglobin content was 11 Gm. per hundred cubic centimeters. Proctoscopic examination showed an edematous mucosa, which was friable and bled on slight trauma and was covered with sanguinopurulent material. Immediately above the sphincter there were a few bleeding polypoid tags.

The course in this case illustrates the tendency to recurrences so frequently encountered in the cases of patients with ulcerative colitis of the chronic variety.

Diagnosis.—The early diagnosis of ulcerative colitis may be rendered difficult if the bloody mucopurulent diarrhea is absent early in the course of the disease. At the onset of the chronic insidious form of this disease, only occasional bouts of diarrhea, with the loss of occult blood, may occur. The early manifestations of the disease in children may be those related to diminution in the appetite, gradual loss of weight and increasing pallor. Such symptoms are nonspecific and are a part of many chronic illnesses. If a history of occasional loose stools or mild abdominal cramplike pains is associated with the symptoms, the index of suspicion is raised. Too often children with such symptoms are not seen until months after the actual onset of the disease, and then only when there is frank blood in the stools. Ulcerative colitis in children should be considered in the differential diagnosis of the condition responsible for unexplained anemia, loss of weight and anorexia.

The identity of ulcerative colitis may be further masked by the appearance of generalized edema, such as was observed in 2 of our cases. With the loss of protein in the stools, with the poor digestion and the failure to absorb foodstuffs from the intestinal tract and with the decrease in intake due to the anorexia, edema simulating that of a nephrotic syndrome may occur because of impaired nutrition or avitaminosis. The replacement of protein material by all routes is rewarded usually with an improvement in the general state of the patient as well as in the local process.

The diagnosis of ulcerative colitis can be made only after exclusion of other causes of diarrhea and colonic bleeding. One must prove the absence of amebas, bacteria of the dysentery-typhoid-paratyphoid group and tubercle bacilli by repeated examination of the stools and of discharges obtained directly from the diseased mucosa. Sigmoidoscopic examination is a valuable aid in making the diagnosis and in charting the progress. Roentgen examinations following the barium enemas may show a normal colonic pattern early in the course of the disease. During the later active stages the roentgenogram usually reveals marked mottling and feathering. During the late healing, fibrotic stage a typical stiff pipelike appearance will be seen.

Other conditions producing bloody stools in children should be ruled out. Aside from the acute and chronic intestinal disorders, one may list duodenal ulceration, polyps, noninfectious granulomas, blood dyscrasias, allergic manifestations in the bowel,[11] diarrhea associated with such deficiency diseases as pellagra, celiac disease and beriberi and occasionally persistent Meckel's diverticulum.

Fever.—As part of the general symptomatology of ulcerative colitis in children, fever is usually present during the active phases. In the chronic variety the fever takes the form of mild elevations of temperature in the evening, with or without chilly sensations. In the more acute phases the temperature ranges from subnormal as a result of medical shock, to very high, as is observed with a fulminating sepsis. In the majority of cases the temperature is highest when the diarrhea is severe.

Laboratory Data.—Aside from the secondary anemia due to chronic loss of blood and infection, the red cell counts in ulcerative colitis are not significant. The variability of the total white cell count from subnormal to high is paralleled by the variability of the neutrophil percentage. Blood cultures are sterile except in the terminal stages, and the agglutination tests of the plasma with various enteric pathogens give negative results. Cultures of feces, of material obtained by rectal swabs and even material from the base of the ulcerations fail to show more than the usual intestinal bacteria.

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11. Rubin, M. I.: Allergic Intestinal Bleeding in the Newborn, Am. J. M. Sc. **200**:385 (Sept.) 1940.

Complications.—Complications during the course of the disease are common. In this series the following were seen:

(*a*) Cutaneous: Pyoderma in the form of furunculosis or deep-seated abscesses was often observed. Presumably, the basic disturbance in tissue nutrition was responsible for the ease of infection.

In 3 cases painful red nodules which simulated the lesions of erythema nodosum appeared on the pretibial regions. The lesions appeared in successive crops, and activity was manifest for four to six weeks. Each lesion went through a typical course, lasting two to three weeks, and the final appearance was that of a contusion. Erythema nodosum complicating ulcerative colitis differed from that ordinarily seen with other infections in that the lesions appeared in successive crops for several weeks. In all cases a tuberculous origin was ruled out by negative reactions to Mantoux tests with high doses of tuberculin. The onset of the cutaneous manifestations in all cases was at a time when the intestinal lesions became active. In 1 case the bulbar and palpebral conjunctivas of both eyes became congested. The ocular changes were associated with involvement of the subconjunctival tissue, which resulted in edema and engorgement of the episcleral vessels. This condition, which lasted about four weeks and subsided spontaneously, has been described in conjunction with erythema nodosum.[12] The occurrence of erythema nodosum as a nontuberculous complication of ulcerative colitis has been described in the case of adults by Bargen [13] and in the case of children by Jackman and associates.[10]

Eczema-like lesions, erysipelas, purpura and pustular lesions were also observed.

(*b*) Gastrointestinal and Intra-abdominal: In 3 cases peritonitis resulted from perforation of the ulcerated colon. This complication, which was uniformly fatal, occurred in the infants with a very acute form of the disease. Cultures of the peritoneal fluid in all cases revealed B. coli as the chief bacterial invader. In cases of the more severe type of the disease the inflammatory process has been found to extend up into the small intestines. In 3 cases in which autopsy was performed, acute ileitis with ulceration was present as a progression of a diffuse ulcerative colitis. In a fourth case the jejunum was also involved by the disease process. A few of the less frequently observed intestinal sequelae include formation of polyps during healing, perirectal abscesses and rectovaginal fistulas following rectal ulceration.

(*c*) Oral: Ulcerations in the oral mucosa and marked dental caries were occasionally encountered.

12. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1735.

13. Bargen, J. A.: Complications and Sequelae of Chronic Ulcerative Colitis, Ann. Int. Med. **3**:335, 1929.

(*d*) In the Respiratory Tract: Complications in the respiratory tract were met with frequently, especially in the form of infection and bronchitis. Pneumonia was usually found as a terminal process.

(*e*) In the Bones and Joints: Clubbing of the fingers and toes, similar to that seen in other chronic diseases, was observed in cases of long-standing ulcerative colitis. Transitory joint symptoms and even full-blown arthritis were found in a few cases during an exacerbation of the disease.

Pathology.—The pathologic process in ulcerative colitis of children as observed through the sigmoidoscope is essentially not different from that seen in adults with the disease. The picture varies considerably from time to time. In the early stages, the mucosa appears acutely hyperemic and edematous, with an excessive secretion of mucus. Miliary abscesses may form throughout the wall of the colon. Together with subsequent ulceration, these changes in the mucosa produce an appearance of granularity. Confluence of the small ulcerations and suppuration yield larger ulcerations. The hyperemic mucosa is friable and bleeds readily on slight trauma. In cases of the acute form of the disease, the necrosis and ulcerations may penetrate all the layers of the intestine and produce perforation. When the process is extensive the subsequent healing by fibrosis produces a thickening of the wall, with a charactristic stiffness of the intestine and contraction of the lumen, which may be demonstrated by the contrast roentgenogram. A further type of healing by excessive granulation may result in the formation of polyps. Strictures have also been described as sequelae of healing. When the ulcerations remain small and superficial, healing may be almost complete or may leave a few pocklike depressions in the mucosa.

In most cases the process at the onset is most extensive in the rectum and the sigmoid flexure of the colon. Extension may occur throughout the remainder of the large bowel and may occasionally pass through the ileocecal valve to the terminal portion of the ileum.

The histologic picture has been described by Buie and Bargen [14] as thrombosis of the smaller vessels, associated with acute inflammation of the mucosa. Subsequently abscesses and ulcers occur. The abscesses are independent of the lymphoid tissue present.

Etiology.—The cause of this disease is still a matter of speculation. Holt and McIntosh [15] stated: "It seems quite possible that the cause of chronic ulcerative colitis is not always the same." The fact that the disease resembles an acute inflammatory process has suggested a bacterial origin. Notable among the bacteria invoked is the diplostrepto-

14. Buie, L. A., and Bargen, J. A.: Chronic Ulcerative Colitis, J. A. M. A. **101**:1462 (Nov. 4) 1933.

15. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton and Company, 1933, p. 298.

coccus of Bargen,[16] which he was able to isolate from specimens obtained both before and after death in cases of ulcerative colitis. Dack and associates[17] isolated Bacterium necrophorum from material obtained during the acute phase of the disease. Thorlakson[18] and later Felsen and Gorenberg[19] pointed out the similarity between chronic recurrent bacillary dysentery and nonspecific ulcerative colitis. On the whole, there is no unanimity of opinion as to there being a specific bacterial causative agent. Many observers have expressed the belief that those bacteria present are secondary invaders. In our cases the cultures both of feces and of exudates from the ulcer bed contained members of the B. coli group and enterococci, which could not be differentiated bacteriologically from the flora of normal colonic tracts. Dysentery organisms were never found, and agglutination tests with various strains gave negative results.

Another possibility suggested is that the disease may represent a Shwartzman phenomenon of the large bowel as a result of previous sensitization to some bacterial toxin.[20]

The psychogenic factor has been cited by some observers.[21] It was observed that many older children did better at home when discharged from the ward. In 1 case, that of a markedly "introspective" 13 year old girl, mental health guidance seemed to have been responsible for a remission in the disease after all other methods were unsuccessful.

Avitaminosis and nutritional disturbances[22] have been blamed, but it is reasonable to believe that they are effects of the disease and do their part in hampering recovery.

In our series of cases there was no one causative factor which stood out.

THERAPY OF NONSPECIFIC ULCERATIVE COLITIS

In considering the therapy of ulcerative colitis, we have excluded the cases in which the outcome was fatal. It was possible to try

16. Bargen, J. A.: Chronic Ulcerative Colitis, J. A. M. A. **83**:332 (Aug. 2) 1924; Arch. Int. Med. **45**:559 (April) 1930.

17. Dack, G. M.; Kirsner, J. B.; Dragstedt, L. R., and Johnson, R.: Bacterium Necrophorum in Chronic Ulcerative Colitis, Am. J. Digest. Dis. **6**:305 (July) 1939.

18. Thorlakson, P. H. J.: Ulcerative Colitis, Canad. M. A. J. **19**:656 (Dec.) 1928.

19. Felsen, J., and Gorenberg, H.: Chronic Dysentery, Distal Ileitis and Ulcerative Colitis, Am. J. M. Sc. **192**:553 (Oct.) 1936.

20. Winkelstein, A.: Etiology and Therapy of Ulcerative Colitis, Am. J. Digest. Dis. & Nutrition **3**:839 (Jan.) 1937.

21. Murray, C. D.: Psychogenic Factors in the Etiology of Ulcerative Colitis and Bloody Diarrhea, Am. J. M. Sc. **180**:239 (Aug.) 1930.

22. McCarrison, R.: Faulty Food in Relation to Gastro-Intestinal Disorders, J. A. M. A. **78**:1 (Jan. 7) 1922.

various forms of treatment in the 15 cases because the patients were observed over a period of years.

As a routine every new patient admitted received courses of emetine hydrochloride, administered parenterally, and antiparasitics by mouth, in order to eliminate the possibility of overlooking amebic colitis.

Nonspecific therapy consisted of the use of transfusions and iron preparations for the anemia; the feeding of high vitamin, high calory, low residue diets, and the administration of camphorated tincture of opium and bismuth by mouth for the abdominal pain and frequency of stools. Repeated small transfusions have been found to be of some benefit to children in combating the anemia and in increasing resistance.

Most authorities recommend a low residue, high vitamin diet. We have found that individualization of the diet is an absolute essential. During the acute stage of the disease the rapid passage of the food through the intestinal tract makes it necessary to administer huge doses of vitamins. These may be given by mouth or by the parenteral route when necessary. The administration of vitamins alone has produced no specific benefits with relation to the basic disease, but it may prevent some of the secondary complications due to avitaminosis. Any item in the diet may be intolerable to a particular child. A low residue diet is usually well tolerated, but in some cases we have noted a marked increase in the number of stools and the abdominal pain after the ingestion of such products as milk and chocolate. In 2 cases a specific food allergy was present. No one set of rules can be applied, but in general it is safe to start with a basic milk-free, spice-free, low residue, high calory, high vitamin diet.

It is well known that there is no specific cure for ulcerative colitis. The ineffectiveness of various therapeutic measures is apparent in the large variety of drugs which have been used. In some cases there seemed to be some benefit from a particular form of therapy, while in others in which the same measure was employed no apparent effect was noted. In 10 cases the patient received sulfanilamide or one of its derivatives, such as azosulfamide or sulfathiazole (2-[paraaminobenzenesulfonamido] thiazole); in 15 cases, rectal instillations of the various irrigating fluids, such as kaolin and aluminum hydroxide, acriflavine (a 1:8,000 solution in physiologic solution of sodium chloride), azochloramid (a 1:2,000 solution in physiologic solution of sodium chloride) and emulsions of cod liver oil.[23] Typhoid vaccine, antidysentery serum and anti-colon-bacillus serum[24] were used in 5 cases.

23. Spiegel, R.: Rectal Instillations of Cod Liver Oil in the Treatment of Ulcerative Colitis, J. Mt. Sinai Hosp. **4**:94 (July-Aug.) 1937.

24. Schwartzman, G., and Winkelstein, A.: A New Type of Serum Therapy for Treatment of Non-Specific Ulcerative Colitis, Am. J. Digest. Dis. & Nutrition **1**:582 (Oct.) 1934.

In 6 cases liver extract was administered parenterally over long periods. Diathermy to the abdomen was tried in 2 cases.

Attention should be given to the question of the mental reaction of young patients to the disease and its treatment. Too often the physician is forced to burden children with ulcerative colitis by greatly restricting the diet, curtailing activity and enforcing prolonged rest in bed in a hospital. If psychologic factors act as predisposing etiologic agents of ulcerative colitis, imposing stern restrictions for years is certainly not helpful. In the pediatric service at Mount Sinai Hospital a policy has been adopted whereby (*a*) hospitalization is employed for a short period and is utilized only during the acute stages of the disease or for the administration of special treatments, (*b*) the diet is varied to minimize the impression of restriction and (*c*) moderate activity is encouraged during the less acute stages. In our experience the child usually does better with care at home, and we have found that the change from the hospital to the home environment is frequently associated with clinical improvement.

We have had little experience with the surgical treatment of ulcerative colitis in children. Surgical intervention should be considered in those cases of the severe type of the disease in which rest, diet and medication have failed to improve the condition of the child and the course is rapidly downhill toward a fatal issue. Of the various surgical procedures that have been tried, ileostomy has been said to offer the best results. With such surgical procedures an attempt is made to sidetrack the fecal stream from the colon in order to put the bowel at rest. Ladd and Fothergill [25] reported 16 cases of ulcerative colitis in children, in which a mortality of 43.7 per cent followed ileostomy. Similar results were obtained by other observers. Aside from the marked inconvenience, such a procedure is not recommended as a routine because of the high mortality and the ultimate failure to obtain a cure in most cases.

In our series of 23 cases there were 8 deaths. Most of the fatalities occurred in the cases of patients under the age of 1 year with the acute type of the disease. The duration of the disease in these cases varied from six days to one year.

Fourteen of the 15 patients who survived were observed for a long period, and the following facts were noted: In 5 the disease showed no symptoms of activity, and the lesions seemed to be healed; in 3 there was improvement, with occasional periods of activity, and in 6 the improvement was slight or absent and there was almost continuous activity.

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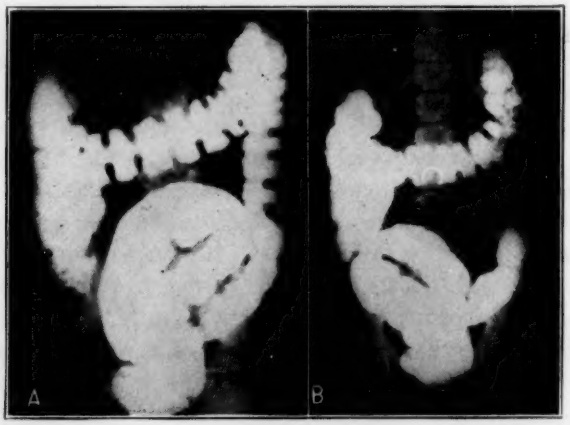
25. Ladd, W. E., and Fothergill, L. D.: Idiopathic Ulcerative Colitis in Children, M. Clin. North America **19**:1673 (March) 1936.

Evidences of healing of the colitis were (*a*) clinical inactivity, as manifested by the absence of anemia, diarrhea and abdominal pain; (*b*) normal results from a sigmoidoscopic examination, that is, absence of inflammatory changes, ulcerations or abscesses and presence of a normal-appearing mucosa with some puckering and coarse granularity at the site of the disease process, and (*c*) normal results from a roentgen examination made after a barium enema was given. The duration of the observation in these cases varied from one and a half to twelve years from the onset of symptoms. We recognize that ulcerative colitis is considered "cured" only after a long period. Three patients are classified as improved but not healed, for they continue to have occasional mild flare-ups of diarrhea, with the passage of mucus or blood-tinged stools and evidence of subsiding inflammatory changes on sigmoidoscopic



A, roentgenogram of R. H., taken Dec. 22, 1939 after a barium enema, reveals an irregularity in the outline of the colon, with some spastic contraction of the descending portion. In the rectum and the sigmoid flexure there is marked loss of haustral markings, indicating involvement. Duration of the disease to date is about four years. *B*, taken Oct. 1, 1940, ten months after *A*. The colon is the seat of progressive involvement. In the sigmoid flexure and the distal portion of the descending colon there is further loss of haustral markings.

examination. These 3 children have been studied for a period of two to four years.

Six of the 14 patients still require vigorous treatment for progressive anemia and frequent bouts of bloody diarrhea associated with abdominal pain. Sigmoidoscopic examinations of these patients reveal all stages of inflammation, ulceration, suppuration and scar formation, with little or no evidence of decreased activity. Roentgen studies made after barium enemas show progression of the involvement of the colonic tract (figure). The duration of the disease in this group has thus far ranged from two to eight years.

Analysis of the data in our cases reveals some facts concerning the ultimate outcome. The extent of the involvement is important. Most complete healing occurred in those cases in which the disease remained localized in the rectum and the lower part of the sigmoid flexure. In those cases in which there was little or no improvement over a period of years it was found that there was more extensive involvement of the rectum, the sigmoid, the colonic tract and even of the terminal portion of the ileum in a few instances. Such changes were observed either during the first attack or during succeeding recrudescences. The number, frequency and duration of recurrences were directly proportional to the extensiveness of the disease. It was strikingly clear that a tendency to healing exhibited early in the course of the disease indicated a better outlook for freedom from future attacks and completeness of healing.

In a few cases the number of recrudescences seemed to be related to the number of infections of the upper respiratory tract. We have the impression that dental caries with alveolar abscesses and infections elsewhere in the body are factors which contribute to the continuation of the activity of the disease process. Care directed to these conditions seems to help to prevent recurrences.

Although the general condition of the child is an index of progress, we have found that clinical quiescence, especially in cases of the more severe type of the disease, is no indication of healing. However, the presence of progressive anemia, with or without the clinical symptoms, is usually indicative of continued activity of the disease and a poorer outlook.

The prognosis in ulceratitve colitis should always be guarded. Too often apparent improvement is only the reflection of a temporary quiescence of the disease, soon to be followed by a recurrence more severe than the last episode. However, one should not assume too pessimistic an outlook at the onset of treatment. Some children respond promptly to treatment; some improve slowly; the condition of others remains stationary or becomes worse, while a few die despite all forms of therapy.

Provided attention is paid to the intake of food and the general health of children with the disease, the basic growth and development will be within normal limits.

SUMMARY

Data from 23 cases in which the disease was diagnosed as nonspecific ulcerative colitis are analyzed. In 8 the patient died. Of the 14 cases in which the patient was observed in the follow-up service, there was

complete healing in 5, improvement in 3 and slight improvement or none in 6. The cause of nonspecific ulcerative colitis is still unknown. The symptoms of the disease are characteristic, the pathologic picture is definite and the results of proctoscopic and roentgenographic examination are typical. Relapses and recurrences are common, and the prognosis must be guarded. At present there is no specific successful form of treatment.

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FURTHER EVIDENCE OF DESTRUCTION OF THIAMINE IN EVAPORATED MILK

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IOWA CITY

Recent observations to the effect that autoclaved whey is lacking in some essential component of the vitamin B complex other than thiamine [1] cast some doubt on the results of a previous study which appeared to indicate that there is a 60 per cent destruction of thiamine in commercial evaporated milk,[2] since in that investigation autoclaved whey was used with the basal ration to supply these other essential constituents. The increased use of evaporated milk, particularly for infant feeding, makes it necessary that the amount of destruction of thiamine be known. The feedings consisting of a mixture of evaporated milk and the usual amount of a vitamin-free carbohydrate, which have a high caloric value, may contain an insufficient amount of thiamine. This may account for the fact that many infants 5 or 6 months of age refuse to take sufficient food for normal gains in weight, even though the usual cereals, fruits and vegetables are offered. Consequently, tests of evaporated milk have been repeated in which the basal ration has included autoclaved yeast, which, with the exception of thiamine, has been shown to contain all the components of the vitamin B complex.

Variations in the amount of destruction of thiamine reported by the different workers who have used autoclaved yeast in the basal ration may be due to incomplete destruction of thiamine in some of the yeast. For the present study three lots of yeast were prepared under conditions which were identical so far as possible. Comparative tests of raw and of evaporated milk were made with each lot by means of the ten day bioassay method, two amounts of yeast, 0.3 and 0.5 Gm. per rat per day, being used. The yeast, a dehydrated powdered product, was prepared by mixing it with distilled water, straining through a fine wire mesh sieve and adjusting to p_H 7 with tenth-normal sodium hydroxide solution. This was then boiled five minutes, allowed to stand twenty-four hours and again brought to p_H 7. After being strained into shallow pans to a

From the Iowa Child Welfare Research Station, State University of Iowa.

1. Daniels, A. L.: Whey as the Substratum in Vitamin B_1 Assays, Proc. Soc. Exper. Biol. & Med. **41**:235, 1939.

2. Daniels, A. L.: Comparison of Vitamin B_1 Content of Raw and Evaporated Milk by the Ten-Day Bio-Assay Method, Proc. Soc. Exper. Biol. & Med. **38**:212, 1938.

depth of ¼ inch (0.64 cm.), it was autoclaved at a pressure of 18 pounds (8.2 Kg.) for six hours; the end product had a p_H of 6.8 to 7. This was then dried in a current of air and subsequently ground. The basal ration consisted of 20 Gm. of a vitamin-free commercial casein,[3] 15 Gm. of autoclaved whey, 47 Gm. of cane sugar, 10 Gm. of hydrogenated cottonseed oil, 3.5 Gm. of cod liver oil, and 4.5 Gm. of the salt mixture of Hawk and Oser,[4] to which copper sulfate was added. This was prepared every two or three days and stored in a refrigerator at a low temperature.

The raw Guernsey milk (containing 4.5 to 5 per cent fat) was obtained from a small local dairy. The evaporated milk tested was the same commercial brand used in the former study. For series 1 and 2, milk marketed in 14½ ounce (429 cc.) tins was used, whereas the 6 ounce (177 cc.) cans were used for the tests in series 3. In all cases

Results of Tests to Determine the Extent of the Destruction of Thiamine in Evaporated Milk

Series	Number of Animals	Milk: Kind	Milk: Amount Fed Daily, Cc.	Daily Supplements: Autoclaved Yeast, Gm.	Daily Supplements: Thiamine Hydrochloride, Micrograms	Weight of Animal, Gm.: Initial	Weight of Animal, Gm.: End	Weight of Animal, Gm.: Gain	Milk for 1 Gm. Gain in Weight, Cc.	Thiamine Destroyed, per Cent
1	2	Raw	8.5	0.5	...	77.3	99.2	21.9	3.9	
	4	Evaporated	12.8	0.5	...	66.8	86.8	20.0	6.4	39
2	5	Raw	9.1	0.3	...	90.4	106.9	16.5	5.5	
	7	Evaporated	12.3	0.3	...	79.5	92.7	13.2	9.3	41
3	13	Raw	8.8	0.3	...	87.8	103.1	15.3	5.7	
	16	Evaporated	14.7	0.3	...	86.1	97.8	11.7	12.6	54
Control animals	A	Evaporated	6.0	0.3	2.8	84.5	95.5	11.0	5.4	
	B	Evaporated	6.0	0.3	3.4	86.9	100.1	13.2	4.5	

the evaporated milk was diluted with 1 part of distilled water. All tests were made between May and October.

In order to make sure that the source of variations in results was inherent in the milk, each series of tests was made with the same batch of autoclaved yeast, so that if all the thiamine in any given batch was not destroyed the effect of that remaining would be constant in a given series. Weighed portions of yeast were added directly to the milk cups and fed first each day. The basal ration was fed ad libitum. Control animals were given diluted evaporated milk in amounts equal to that used for the tests with Guernsey milk. With this, two amounts of thiamine hydrochloride were used, 2.8 micrograms and 3.4 micrograms per rat per day.

3. The casein used was the Labco brand produced by the Borden Company Research Laboratories.

4. Hawk, P. B., and Oser, B. L.: Science **74**:369, 1931.

The results for all groups, which are summarized in the table, indicate considerable destruction of thiamine in the evaporated milk: 39 per cent for series 1, 41 per cent for series 2 and 54 per cent, only slightly less than that reported in a previous paper, for series 3. Tests with the control animals indicate that the difference in the results with the raw and with the evaporated milk is due to the smaller amount of thiamine in the evaporated milk. The addition of 2.8 micrograms of thiamine hydrochloride to 6 cc. of diluted evaporated milk resulted in a gain in weight per cubic centimeter of milk fed comparable to that of the animals fed raw Guernsey milk, whereas the addition of 3.4 micrograms of thiamine hydrochloride resulted in a 16 per cent increase in weight. In series 1, in which 0.5 Gm. of autoclaved yeast was used, the amount of milk required for 1 Gm. of gain was less in each case than in series 2. The percentage difference, however, is the same. Either this particular batch of yeast contained slightly more thiamine or more was supplied by the larger amount of yeast used.

It should be noted that the amount of raw milk required for a 1 Gm. gain in weight was practically the same in series 2 and series 3, in which 0.3 Gm. of yeast was used, as in the previous study, in which the basal ration contained no yeast, whereas the amount of evaporated milk needed for such a gain in series 3 (12.6 cc.) is somewhat higher than that required in series 2 (9.3 cc.). This possibly may be due to longer processing of the 6 ounce tins in proportion to the amount of milk treated. In the previous study, however, in which slightly greater destruction of thiamine was observed (60 per cent), 14½ ounce cans were used. It seems, therefore, that the thiamine content of commercial evaporated milk is not constant, and in the brand tested the proportion destroyed may vary from 39 to 60 per cent. The smaller amount of the vitamin in evaporated milk should be borne in mind when a diet high in thiamine is desired.

Case Reports

ANOCOCCYGEAL CYST

HOWARD LORENZ, M.D.
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Because of the rarity of the condition, the following case of congenital anococcygeal cyst is reported.

REPORT OF A CASE

S., a newborn girl, delivered by Dr. Charles S. Wachs on Dec. 29, 1940, had an unusual anomaly. Projecting from the anococcygeal region was a large sac covered by skin. The anus was relatively small but intact; the sphincter ani responded to external stimulation, and the bowels moved normally. From the posterior anal margin and from the area 1 cm. to the right and 2 cm. to the left of the anus the skin projected away from the body to form the anterior wall of the neck of the sac. The skin from the sacral region and the medial aspect of the buttocks formed the posterior and lateral walls. The neck of the sac was 2 cm. long, and from it the skin ballooned out to form a sac 13 by 10 by 8 cm. On palpation the contents appeared to be fluid. Light was easily transmitted and disclosed several veins; the main one, derived from several branches, traveled posteriorly. On the lateral aspect were several smaller veins. Areas of varying density were apparent in the skin covering the anterior wall. Examination of the sac also disclosed (1) two nevi, one 3 by 4 cm. and the other 1 by 1 cm.; (2) a dipping in of the skin along one side near the neck of the sac, and (3) an area 2 by 0.5 cm. which looked like an old blood clot. When the infant cried the sac did not change in contour or position. In other respects the child was apparently normal. The legs showed no limitation of motion.

On December 30, the day after delivery, the entire sac was amputated by Dr. Moses Behrend. The report of the operation follows: "With the patient under local anesthesia and in the prone position, a large congenital cyst was excised from the region of the coccyx. This cyst contained clear fluid and was probably a meningocele. The skin over the coccygeal region was sutured tightly by means of several interrupted dermal sutures. A collodion dressing was applied. No communication between the spinal canal and the cyst could be demonstrated."

Dr. Samuel Levine examined a portion of the tissue microscopically and gave the following report: "The section of tissue is lined by squamous stratified epithelium having a sharp line of demarcation. The stratum corneum shows hypertrophy. The rete pegs are shallow. A number of lymphatics, hair follicles and sebaceous glands are seen in the dermis. There are numerous blood vessels and some areas of fatty tissue."

From the Obstetric and Surgical Services of the Jewish Hospital.

Fig. 1.—Anterior view of the patient.

Fig. 2.—Posterior view of the patient.

Fig. 3.—Roentgenogram, anteroposterior view, showing no abnormality.

COMMENT

No similar case was found in the literature of the past decade.[1] Review of the theories of the origin of sacrococcygeal cysts indicates that such cysts may represent vestiges of the neurenteric canal or of the postnasal gut or raphe inclusions.

The photographs were taken by Morris Skarupsky, resident x-ray technician and photographer of the Jewish Hospital.

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1. Thomason, T. H.: Cysts and Sinuses of the Sacrococcygeal Region, Ann. Surg. **99**:585-592 (April) 1934. Ravin, R. W.: Sacrococcygeal Cysts and Tumors, Brit. J. Surg. **23**:337-361 (Oct.) 1935. Guis, J. A., and Stout, A. P.: Perianal Cysts of Vestigial Origin, Arch. Surg. **37**:268-287 (Aug.) 1938.

GANGRENE OF THE EXTREMITIES IN THE NEWBORN

OCCURRENCE OF FUNCTIONAL RECOVERY

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AND
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ENGLEWOOD, N. J.

Gangrene of the extremities is one of the most unusual disabilities observed in the newly born infant. Study of the literature reveals a total of only 39 recorded cases, of which only 4 were reported by physicians in the United States.

We present in this paper the report of a case of gangrene of this type, which was observed by us in the Englewood Hospital, and a concise review of the literature. On the basis of the observations in our case and the results of others, we shall try to evaluate the causative factors which are involved and to indicate the therapeutic procedure which seems to offer the best chance of effecting satisfactory functional recovery.

REPORT OF A CASE

J. B., a boy born July 7, 1940, weighed 9 pounds 7 ounces (4,281 Gm.) at birth. The father was 27 and the mother 26 years of age; they were of Danish and Irish ancestry respectively. The mother had always been well and had no trauma or severe illness during pregnancy. Her reaction to the Kline test was negative. The patient, the result of her first pregnancy, was born at term. The baby's position was recorded as being right occipital transverse. After twenty-nine hours of labor, because of maternal exhaustion, a midforceps operation was employed to effect delivery. The analgesic agents used were 6 grains (0.39 Gm.) of pentobarbital sodium and drop ether at the time of delivery. It was noted at birth that the baby's condition was poor. He was deeply cyanotic and, according to the intern who assisted at the delivery, he did not breathe for over ten minutes. Mouth to mouth insufflation was employed, and rhythmic breathing was finally established.

On July 8, the day after birth, the baby weighed 8 pounds 14 ounces (4,026 Gm.). His color was poor, there was a large excoriation on his left cheek caused by the forceps, his right arm was paralyzed and his right hand was cold, limp and blue. His face was edematous.

On July 9 his face looked better and he weighed 8 pounds 7 ounces (3,827 Gm.). The impression of the hospital staff was that his wrist was broken because it was held so limply, and ecchymoses were observed on both sides of it. That evening his temperature rose to 104 F., and soon afterward we examined him. Our observations recorded at that time were: cephalhematoma, bruise on the face (an excoriated area 4 cm. in diameter), lack of pulsation of the right axillary

Fig. 1.—Appearance of forearm when the patient was 7 days of age.

Fig. 2.—Appearance of forearm when the patient was 26 days of age.

and radial arteries and spasticity of the right arm and forearm but complete flaccidity of the right hand. The upper part of the right arm was swollen and purplish red, but the hand was practically white; the baby was moderately dehydrated. Our impression was that of: (1) dehydration fever, (2) injury to the right brachial plexus (?), (3) moderate intracranial damage and (4) arterial stasis of the right upper extremity due to sympathetic injury or thrombosis.

The following day the baby was still moderately dehydrated. Lateral nystagmus was noted. A spinal puncture revealed blood-tinged fluid under low pressure. Later that day the baby had several convulsions, at first with twitching of the left arm and leg with severe nystagmus; still later, when the temperature was 104.4 F., there was a severe convulsion which involved practically the entire body with the exception of the right arm.

On July 11 the baby weighed 8 pounds 12 ounces (3,969 Gm.), a gain of 5 ounces (142 Gm.), and he looked better. The following day he weighed 9 pounds 5 ounces (4,224 Gm.), and gangrene involving practically the whole right upper extremity below the elbow was observed. At this time there was some question in our minds whether amputation would not be advisable, because it seemed that gross necrosis would eventuate and that danger from absorption and sepsis could best be avoided by such a procedure. Temporization was decided on, and we applied flannel dressings with external heat and elevation of the extremity. No further treatment was employed except that later, when vesicles formed and ruptured, the dry dressing was changed to simple boric acid ointment and, except for the removal of slough which appeared at the surface, the arm was left strictly alone.

During the baby's second week of life his temperature reached 101 F. daily. After that time it remained within normal limits.

The baby remained in the hospital for two months. Pulsation of the axillary artery was first palpable on July 13, six days after birth. The radial pulse was first palpable on July 19, twelve days after birth. Beginning necrosis of the gangrenous area was first noted on July 17. On July 19 the baby was able to move his forearm and fingers for the first time. On July 24 fair function of the extremity was observed. From this time on the condition improved steadily. On August 24, forty-eight days after birth, the following note was written:

"At the present, except for some exuberant granulations, the draining areas are healed. At no time has there been true infection. What drainage there has been was of necrotic origin. How much muscle loss has occurred is not certain now. There is some atrophy of the right forearm, the carrying angle appears increased and the fingers are held somewhat flexed. Perhaps mechanical extension may later be needed, but at present it is believed that passive motion will help, and we are afraid that the skin might not bear the amount of tension required for mechanical extension.

"Measurements of the two upper extremities made on three occasions have shown considerable atrophy of the forearm, but when the baby was last seen there seemed to be no single muscle which was not functioning well, and he used his right hand well."

Laboratory Data.—A roentgenogram of the right upper extremity made July 9 showed no evidence of fracture or abnormality of the joint relations. The bone markings were clearcut, and there was no evidence of a cervical rib. The heart and lungs seemed normal.

Repeated urinalyses showed nothing unusual except for a few leukocytes on July 24.

TABLE 1.—*Clinical Data for the Forty Recorded Cases of Gangrene of the Extremities in the Newborn*

Case No.	Author	Age, Days	Part Involved	Therapy	Result	Cause	Delivery
1	Martini: Mag. f. d. ges. Heilk. **27**: 428, 1828	8	Both legs	External applications	Death	?	Easy
2	Richter: Expérience **2**: 442, 1838; **3**: 193, 1839	?	Spots on extremities	—	?	?	?
3	Leopold: Arch. f. Gynaek. **10**: 189, 1876	15	Both legs	—	Death	Thrombi	Difficult; asphyxia
4	Ahlfeld, cited by Leopold	9	Right leg	Amputation	Death	?	?
5	Weickert, cited by Leopold	10	Both legs	—	Death	Pyemia	?
6	Manlay: Lancet **2**: 1173, 1888	Prenatal	Both hips and all areas below	—	Death	Pressure	Breech; child gangrenous before delivery
7	Theodor: Arch. f. Kinderh. **15**: 358, 1893	14	Vulva and legs (superficial)	Incision of bullae	Recovery	Infection	Normal
8	Finkelstein: Berl. klin. Wchnschr. **32**: 496, 1895	10	Generalized	—	Death	Septicemia	Extraction; puerperal sepsis
9	Durante: Méd. inf. **2**: 222, 1899	17	Both feet	—	Death	Raynaud's disease (?)	?
10	Durante: Méd. inf. **2**: 222, 1899	24	Lower part of abdomen; thighs	—	Death	Syphilis (?)	?
11	Mueller: Ueber Gangrän von Extremitäten bei Neugeborenen Inaug. Dissert., Strassburg, C. & J. Goeller, 1899	Birth	Left forearm	Amputation	Death	Pressure	Difficult; brow presentation
12	Freund: Verhandl. d. deutsch. Gesellsch. f. Gynäk. **8**: 500, 1899	Birth	Left hand	Amputation	Recovery (?)	Pressure	Easy extraction
13	Veillon and Hallé: Ann. de dermat. et syph. **2**: 401, 1901	4	Generalized	—	?	Bacteremia	?
14	Bowes: Lancet **2**: 586, 1901	16	Spread from lumbar region	Dilute lysol dressings	Death	?	Normal
15	Cotes-Preedy: Lancet **1**: 575, 1904	Birth	Right leg	—	Death	Trauma to mother (?)	Normal; child born with cord about neck
16	Foltanek: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **5**: 191, 1906	8	Foot	?	Recovery (?)	?	?
17	de Bruin: Nederl. tijdschr. v. geneesk. **2**: 1349, 1906	Birth	Right leg	Autoamputation	?	Syphilis or thrombi (?)	?
18	Haverschmidt: Jahrb. f. Kinderh. **65**: 624, 1907	1	Soles	—	Recovery	Meningomyelocele	?
19	Kosmak: Bull. Lying-in Hosp., New York **4**: 124, 1907	10	Both legs; both hands	—	Death	?	Prolonged labor

20	Winslow: Tr. South. S. & Gynec. A. **24**: 208, 1911	3	Right forearm	Amputation	Recovery	?	Normal
21	Wieland: Deutsche Ztschr. f. Chir. **116**: 783, 1912	14	Tips of two fingers	Incision of necrotic tissue	Recovery	Paronychiae	Difficult extraction
22	Fitzwilliams and Vincent: Lancet **1**: 753, 1913	10	Right leg	Amputation	Recovery	?	Normal
23	Loewy: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **21**: 153, 1922	5	Toes	—	Recovery	?	?
24	Castana: Pediatria **31**: 1305, 1923; cited by Barmwater	Birth	Left arm; toes	(?)	Recovery; loss of forearm	Sympathetic neuritis (?)	(?); asphyxia livida
25	Hoopman and Grant: M. J. Australia **1**: 288, 1924	14	Both feet	—	Death	Thrombi	Normal
26	Barmwater: Wien. klin. Wchnschr. **38**: 220, 1925	Birth	Both hands; both legs	—	Death	Raynaud's disease	Normal; congenital cardiac anomaly
27	Grove: Brit. M. J. **1**: 738, 1926	7	Right foot	—	Recovery; loss of toes	Embolus (?)	Normal
28	de Snoo: Nederl. tijdschr. v. geneesk. **72**: 3915, 1928	3 (?)	Skin of right foot	?	Recovery	Vasomotor disturbance	Difficult; asphyxia
29	Fischer: Arch. f. Gynäk. **136**: 181, 1929	7	Right forearm	—	Death	Thrombus	Difficult; hand over brow
30	Grassi: Riv. di clin. pediat. **29**: 120, 1931	10	Right forearm	—	Recovery; loss of forearm	Trauma at delivery	(?); asphyxia
31	Obadalek: Arch. f. Kinderh. **90**: 111, 1930	14	Left leg	—	Recovery	?	Normal
32	Lawrence: Arch. Dis. Childhood **6**: 343, 1931	15	Right hip and wrist; left ankle	Dietary	Recovery	Diabetes (?)	Normal
33	Corret: Rev. méd. de l'est **60**: 64, 1932	12	Lower part of leg	Amputation	Recovery	Periarteritis; thrombi	?
34	Dohan: J. Pediat. **5**: 756, 1934	13	Left foot	Amputation	Recovery	?	Normal
35	Hallé and Leveuf: Bull. Soc. de pédiat. de Paris **22**: 523, 1934	4	Dorsum and toes of right foot	Elevation; warmth	Recovery	Infection	Normal
36	Lévy: Monde méd. **49**: 542, 1939	1	Right foot; spot on buttock	Balsam of Peru	Recovery	?	Normal
37	Lévy: Monde méd. **49**: 542, 1939	9	Left leg	Amputation	Recovery	?	Forceps; moderately difficult
38	Huber; Florand and Payet: Bull. Soc. de pédiat. de Paris **37**: 54, 1939	21	Tips of two fingers of each hand	—	Recovery; some slough	Raynaud's disease (?)	Normal
39	Barbé, cited by Huber, Florand and Payet: Bull. Soc. de pédiat. de Paris **37**: 54, 1939	18	Six fingers	—	Death	Raynaud's	Normal
40	Heller and Alvari	Birth	Right forearm	Elevation; warmth	Recovery	Pressure	Difficult; asphyxia

On July 17 a blood count showed a hemoglobin content of 94 per cent, 4,200,000 red cells and 9,000 white cells, 81 per cent of which were polymorphonuclear. On July 16 a culture of material from the gangrenous area showed Staphylococcus albus.

Measurements of Upper Extremities.—The following measurements of the right and left arms were obtained:

	August 28 (Age, 7 Weeks)			October 5 (Age, 13 Weeks)			November 16 (Age, 18 Weeks)		
	Right	Left	Difference	Right	Left	Difference	Right	Left	Difference
Subaxillary circumference, cm....	11.0	11.5	0.5	13.0	13.0	0.0	14.5	14.5	0.0
Circumference above elbow, cm..	10.6	11.0	0.4	10.8	11.4	0.6	12.8	13.2	0.4
Circumference of middle of forearm, cm.....	9.5	10.5	1.0	....	....	...	....	....	...
Circumference of upper third of of forearm, cm.....	....	....	...	10.0	12.4	2.4	10.8	13.8	2.0
Circumference of wrist.....	7.8	9.2	1.4	8.0	9.7	1.7	8.6	10.6	2.0
Circumference of hand.....	...	...	...	...	...	...	9.7	10.5	0.8

TABLE 2.—*Résumé of Data for Forty Cases of Gangrene in the Newborn*

Part involved:	
Upper extremity	9
Lower extremity	24
Scattered	7
Result:	
Death	16
Recovery with gross mutilation	9
Functional recovery	10
In doubt	5
Causative factor:	
Presumably pressure	5
Presumably infection	6
Presumably Raynaud's disease or other neurologic disorders	7
Thrombi	4
Syphilis	1
Trauma to mother	1
Diabetes mellitus	1
No definite assumption as to cause	15
Type of delivery:	
Difficult	14
Normal	14
In doubt	12

COMMENT

Including the case we are reporting, we have assembled a total of 40 cases of gangrene in the newborn. In table 1 are presented the essential facts regarding these cases, and in table 2 there is a brief résumé of the data for them. From the figures noted and from the authors' own words, a few definite conclusions may be drawn. The cases fall roughly into two categories: those in which the gangrene seems definitely referable to pressure associated with long and difficult delivery and those in which it is due to infection. In a number of the cases in which a neurologic disorder, such as Raynaud's disease, was suggested by the author as the causative factor, the diagnosis is open to considerable doubt. Most of the writers admitted this. In addition, several of the diagnoses, notably that of diabetes mellitus, which was reported by Lawrence in 1931, are based on evidence which is not conclusive. It may be noted that the incidence of hard and difficult labor and the percentage occur-

rence of neonatal asphyxia are far in excess of that encountered in any routine series of deliveries.

In those cases in which the disorder was caused by infection, the diagnosis reached and the therapy given are in no way open to criticism. It is reasonable to believe that if treatment were given in a similar group of cases at this time there would be a lower mortality rate because sulfanilamide and its derivatives are now available as tools.

With regard to the group of cases in which the condition seemingly was caused by pressure and those in which the cause presumably was Raynaud's disease or some other neurologic disturbance, especially the cases in which the delivery of the patient was long and difficult, we believe that our experience in the case here reported permits a reasonable hypothesis regarding the cause of this type of gangrene, and conclusions concerning the superiority of conservative treatment over early amputation. We believe that in this case there is no likelihood of there having been true thrombus formation. Had such existed it would have been impossible to establish canalization in so short a time, and freeing of a thrombus would have resulted in a more dramatic episode distal to the axillary artery than that which occurred. We need not assume rapid establishment of collateral circulation, because we know that the axillary artery itself resumed pulsation in a comparatively short time. Our assumption, which, we believe, though novel is supported by the child's progress, is that there existed a temporary agglutination of the intimal surfaces of the large vessel similar, one might say, to that which occurs when a piece of rubber tubing of equivalent caliber is pressed on firmly for a protracted period. Perhaps the surfaces were sealed with fibrin, which essentially shut off all distal supply of blood but was not necessarily accompanied by thrombus formation. When the pressure was no longer a factor, the proximal pulsating blood stream acted as a hydrostatic wedge, and the adhered surfaces gradually were forced apart and circulation again established soon enough to preserve function but not before a modicum of damage had been done. We believe that in the majority of the cases reviewed in this report there may well have been just such a cycle, even in those in which a diagnosis of gangrene of neuropathic origin was made. Certainly, it is most illogical to assume that in a tiny baby Raynaud's disease would follow a course of this sort, which it never follows in patients at any later period of life. Accordingly, we believe that when this extremely rare condition occurs it might be well for the obstetrician or the pediatrician, in the absence of gross infection, to consider the likelihood of intimal adhesion's being the essential factor involved and not to adopt such a mutilating procedure as amputation unless survival without it is believed impossible.

Although this review is concerned only with cases of gangrene of the extremities in newly born infants, it is worth while to compare this small group of cases with the cases of gangrene of this type in older children.

Von Khautz,[1] of Vienna, assembled in 1914 a group of 50 cases of gangrene in children; the patients varied in age from newly born infants to children of 15 years. Although his data are rather sketchy and no accurate figures regarding the ages of the patients are presented, some of his figures are worth mentioning.

Of the entire group of 50 cases, in 39 gangrene followed acute infections, distributed as follows: diphtheria and typhoid fever, 6 each; scarlet fever, 5; syphilis, 5; measles and enteritis (?), 4 each; typhus, 3; pneumonia and omphalitis, 2 each; angina, 1, and fever of unknown origin, 1. In 4 of the 11 cases in which the disorder was of noninfectious origin the cause was given as Raynaud's disease, in 1 chlorosis was held responsible and in 6 the cause was not positively known.

In 16 of his 50 cases the disease occurred in infancy, but the ages of the patients in this group and the upper age limit of *Säuglingsalter* are not given. Besides the infants, there were 2 or 3 patients of almost every age up to 15 years.

In his cases 21 patients recovered, 16 died and for 13 he did not know the outcome; but he assumed that a 50 per cent mortality in his series would be no exaggeration.

Von Khautz speculated considerably regarding the possible causes of gangrene, and his classification included: (1) primary thrombosis, usually following infection; (2) secondary thrombosis, following either injury or intrinsic inflammation of the artery (so-called arteritis toxica); (3) emboli; (4) endarteritis obliterans, and (5) neurotic angiosclerosis.

He mentioned in his article the idea of rupture of the intima, which was described by Hofmann and also by Von Amussat, and this theory must be considered in the case that we are reporting.

We have not attempted to give von Khautz's splendid bibliography in full, but it is most exhaustive and may be referred to profitably by any one who is interested in gangrene of the extremities in older children.

SUMMARY

A case of gangrene of the upper extremity in a newborn child has been reported.

The literature concerning 39 similar cases has been reviewed.

Certain conclusions regarding the causative factors have been discussed and a new theory as to cause, namely, "intimal agglutination," advanced.

Evaluation of the results of conservative therapy as opposed to those of early amputation has been attempted.

Dr. Cleland Cochrane, of the maternity service of the Englewood Hospital, helped to assemble the data pertaining to the case, and Dr. Thomas Protzman took the photographs.

1. von Khautz: Ztschr. f. Kinderh. **11**:35, 1914.

ATRESIA OF THE TERMINAL PORTION OF THE ILEUM, WITH PERFORATION, IN A PREMATURE INFANT

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Atresia or stenosis of the intestinal tract is estimated to be present in about 1 of 20,000 newborn children. Hunt [1] was able to collect from the literature about 500 cases of congenital obstruction between the pylorus and the rectum. These reports, however, also included all cases of obstruction due to such abnormalities as developmental bands or membranous outgrowths, tumors of the intestinal wall, mucus plugs volvulus and intussusception. Ladd [2] has reported the largest single series, 40 cases from the Children's Hospital in Boston. According to Glover and Hamann [3] these abnormalities are due (1) to errors of rotation and failure of fusion and (2) to defects in intrinsic development producing atresia, stenosis or actual interruption of continuity. Atresia occurs with greatest frequency in the esophagus, next most frequently in the distal half of the duodenum and the upper part of the jejunum and rarely in the terminal portion of the ileum. Aird [4] explained that during the embryonic period these sites are under longitudinal strain which may result in thinning out of the walls and obliteration of the lumen of the esophagus and the gastrointestinal tract.

Atresia of the terminal portion of the ileum is exceedingly rare. Surgical intervention has been attempted many times, but up to June 1940 only 4 cases had been recorded in which operation was successful (Fockens, Demann, Carter and Goldberg [5]). Perforation of the gastrointestinal tract before and shortly after birth also is rare; the prognosis

1. Hunt, H. B.: Roentgenological Aspects of Congenital Small Colons and of Intestinal Occlusions, Am. J. Roentgenol. **41**:564-574 (April) 1939.

2. Ladd, W. E.: Congenital Obstruction of the Small Intestine, J. A. M. A. **101**:1453-1458 (Nov. 4) 1933.

3. Glover, D. M., and Hamann, C. A.: Intestinal Obstruction in the Newborn Infant Due to Congenital Anomalies, Ohio State M. J. **36**:833-840 (Aug.) 1940.

4. Aird, I.: Notes on the Surgery of the Newborn: The Foetal Atresiae, Tr. Med.-Chir. Soc. Edinburgh, 1938-1939, pp. 174-184; in Edinburgh M. J., November 1939.

5. Fockens, Demann, Carter and Goldberg, cited by Stenson, W.: Duodenal Occlusion in the Newborn, Am. J. Dis. Child. **56**:1066-1081 (Nov.) 1938.

is uniformly bad (Thelander and Mathes,[6] Medearis[7] and De Vel[8]). Careful search of the literature did not reveal any case of atresia of the terminal portion of the ileum with perforation in a premature infant. Therefore it was felt justifiable to report the following case.

REPORT OF A CASE

The patient's mother was a 29 year old primipara with a noncontributory personal and family history and a negative reaction to a Kahn test on the blood. Onset of the last menstrual period was May 1, 1940. The expected date of delivery was Feb. 8, 1941. The gestation period was normal except for nausea and vomiting during the first trimester.

On December 15 the mother slipped on the icy street and instantly felt a sharp pain in the lower part of the abdomen. Two hours later labor pains started, and when she was examined at the hospital labor was well in progress. The cervical os was dilated about 4 cm. Four hours after the beginning of labor the mother was delivered of a premature male infant weighing 4 pounds 6 ounces (1,984 Gm.). On physical examination the infant appeared normal except that the respirations were irregular and he was slightly cyanotic. Oxygen and carbon dioxide were administered. The respirations became regular, and the cyanosis disappeared.

The infant tolerated dextrose water well. Twelve hours after delivery he was given a milk formula which was completely regurgitated. It was noticed that fifteen hours after delivery there had been no bowel movement, but three hours later a small meconium stool was passed. A consultation was requested, and frequent feedings were instituted. It was noticed, however, that the feedings of milk were all regurgitated, although the baby continued to retain the dextrose water. Twenty-four hours after delivery the infant's temperature rose to between 99.4 and 101.8 F. On the second day the baby had passed only meconium stools. Magnesia magma was given. At this time distention of the abdomen was first noticed. An enema of a solution of sodium bicarbonate was given, without results. A Levine tube passed into the stomach seemed partially to decompress the abdomen. There were no more meconium stools after December 17. On December 18 the distention became more marked and all feedings were regurgitated. A catheter was inserted into the rectum, but neither flatus nor feces were expelled. Gastric lavage revealed the presence of fecal particles. Marked generalized icterus appeared. The abdomen became more and more distended, and the baby died on the fourth day post partum.

Autopsy.—The body was that of a premature male infant weighing 3½ pounds (1,534 Gm.). The skin and the scleras were deeply icteric. The mucous membranes were pale. Little subcutaneous fat was present. There was marked distention of the abdomen. The skin was dry and in folds. When the abdomen was opened a foul-smelling gas escaped under pressure. There was 1 ounce (30 cc.) of greenish, foul-smelling fluid in the peritoneal cavity. The stomach, duodenum,

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6. Thelander, H. E., and Mathes, M.: Duodenal Perforation in a Newborn Infant, Am. J. Dis. Child. **57**:596-602 (March) 1939.

7. Medearis, D. N.: Spontaneous Rupture of the Intestine in the Newborn Infant, Am. J. Dis. Child. **45**:115-117 (Jan.) 1933.

8. De Vel, L.: Intestinal Perforation with Pneumoperitoneum in the New-Born Infant, Am. J. Dis. Child. **45**:587-589 (March) 1933.

jejunum and ileum were markedly distended and dark red, and there was a perforation about 5 cm. above the ileocecal valve. A plastic fibrinous exudate covered the lower part of the ileum for about 10 cm. There was a large mesenteric lymph node about the size of a hazelnut near the perforation. Examination showed complete atresia of the ileocecal valve. The colon was contracted throughout to the size of a lead pencil; the lumen was patent throughout. The pylorus was patent, and the liver and the gallbladder were normal, as were the pancreas, the kidneys, the adrenals, the ureters and the bladder. The pericardium contained a small amount of clear, straw-colored fluid. The heart was normal in size and appearance. The pleural cavities were free of fluid, and both lungs were well aerated. The thymus measured about 7 by 2 by 1 cm. and was of normal consistency.

Anatomic Diagnosis.—The anatomic diagnosis was congenital atresia of the ileocolic valve, perforation of the lower part of the ileum, with localized peritonitis and lymphadenitis, and pneumoperitoneum.

COMMENT

The most important diagnostic sign of occlusion of the gastrointestinal tract in a newborn infant is persistent vomiting, starting soon after birth. If further confirmation is needed a flat roentgenogram or a roentgenogram taken after administration of barium sulfate will either show stenosis or reveal free gas in the upper part of the abdomen if a perforation is present. Since the prognosis even for full term infants with perforation of the gastrointestinal tract is invariably fatal, it did not appear justifiable to make any roentgen examination of this premature infant. He was left in the incubator all the time. It was believed that the stenosis was in the distal part of the intestinal tract since dextrose water was retained and milk was regurgitated at the first feeding.

The diagnosis of occlusion can be verified without a roentgenogram because the meconium of an infant with atresia does not contain stratified epithelium, which is present in normal meconium stools. Unfortunately, no bacteriologic study was done in this case. Thelander and Mathes [6] found Bacillus coli, and Barnum and Moore [9] found Aerobacter aerogenes in their cases of intestinal perforation. The perforation in the present case might be explained on the basis of increased peristalsis just above the stenosis followed by thinning of the intestinal walls and bacterial invasion.

SUMMARY

The case of a premature infant is reported in which there were atresia of the terminal portion of the ileum and perforation 5 cm. proximal to the atresia, followed by peritonitis, pneumoperitoneum and death.

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9. Barnum, C., and Moore, M. R.: Localized Acute Enteritis with Perforation and Peritonitis, J. Pediat. **15**:572-573 (Oct.) 1939.

THE WATERHOUSE-FRIDERICHSEN SYNDROME

REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH AUTOPSY

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The earliest report of the condition now known as the Waterhouse-Friderichsen syndrome appeared in 1894, when Voelcker [1] described it as a fulminating purpura in conjunction with bilateral adrenal hemorrhage. The term Waterhouse-Friderichsen syndrome is derived from the names of the two investigators who reported cases of the malady, reviewed the literature and postulated a possible bacterial causation.[2]

FEATURES OF THE WATERHOUSE-FRIDERICHSEN SYNDROME

Etiology.—The meningococcus is recovered from the blood stream in at least 60 per cent of the cases. Other offending organisms include Streptococcus haemolyticus and rarely the pneumococcus. The blood culture is not infrequently apparently sterile.

Along these lines it is interesting to note that both the meningococcus and the pneumococcus are ectodermotropic and attack the skin, the central nervous system and the adrenal medulla. As will be seen later, this characteristic helps to elucidate some of the clinical signs of the disease.

Clinical Course.—The course resembles in all respects that of a fulminating type of meningococcic septicemia. It is almost unbelievably rapid. The patient has usually been in perfect health until the onset of the illness, some two or three hours previous to being seen by the physician. There may be hyperpyrexia but no characteristic signs or symptoms aside from a rapidly developing purpuric eruption which is widely distributed over the skin and mucous membranes. Intense cyanosis of the nail beds and the lips soon follows. The rapid spread of the purpuric lesions soon leaves only a small portion of the patient's body unaffected.

1. Voelcker, A. F.: Pathological Report, Middlesex Hosp. Rep., 1894-1895.

2. Waterhouse, R.: A Case of Suprarenal Apoplexy, Lancet **1**:576, 1911. Friderichsen, C.: Nebennierenapoplexie bei kleinen Kindern, Jahrb. f. Kinderh. **87**:109, 1918.

Fleeting signs of pulmonary involvement are occasionally described, but the presence of such involvement is not verified by postmortem examination. The blood pressure usually falls, and the patient may die in circulatory collapse in four to forty-eight hours.

Laboratory Data.—Blood culture yields the meningococcus in 60 per cent of the cases, while in the remaining 40 per cent the hemolytic streptococcus, the pneumococcus or no organism is recovered.[3] In some cases the offending organism has been identified in the routine differential blood count. The probability of identification by this method is materially increased if the blood for the count is taken at the site of a purpuric cutaneous lesion.

Examination of the cerebrospinal fluid reveals no constant alterations either in the cytologic or in the chemical components. The cell count may be high enough to impart turbulence to the fluid, but rarely, if ever, is the fluid frankly purulent. Bacteriologic study of the spinal fluid is less frequently informative than is blood culture.

Pathologic Changes.—The chief lesions of note are the petechiae and the purpuric ecchymoses on the skin and the mucous membranes and the massive adrenal hemorrhage. Microscopically, the cutaneous lesions are seen to be due to direct involvement of the capillaries and the arterioles by the causative organism. The adrenal hemorrhage may be of pinpoint size, but most frequently there is massive hemorrhage into the medulla and the zona reticularis, from which it apparently diffuses into the other layers of the gland. There is rarely any evidence of thrombosis, embolism or inflammation.[4]

The brain usually shows congestion of the superficial vessels of the leptomeninges. Frank signs of meningitis are characteristically absent.

Too frequently to be incidental, hyperplasia of the thymus and the other lymphatic structures of the body is associated with this syndrome. For example, in reporting 11 cases in 1901, Little[5] noted that Peyer's patches were much swollen and unusually prominent, "as in the early stage of typhoid," and that in addition the mesenteric glands were enlarged in 6 cases; the thymus was described as enlarged in 2 cases. This is all the more interesting in the light of recent work in the field of adrenal pathology which has indicated a rather close correlation between adrenal hypoplasia and status thymicolymphaticus, or prominence of the thymus and the lymphatic structures.

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3. Usher, S. J.: Adrenal Hemorrhage (Waterhouse-Friderichsen) in a Young Child, Canad. M. A. J. **38**:232, 1938.

4. Levinson, S. A.: Waterhouse-Friderischen Syndrome, J. Pediat. **14**:506, 1939.

5. Little, E. G.: Cases of Purpura Ending Fatally Associated with Haemorrhage into the Suprarenal Capsules, Brit. J. Dermat. **13**:445, 1901.

Treatment.—At best therapy is only supportive. It consists of infusions of physiologic solution of sodium chloride, large doses of adrenal cortical extract with epinephrine to increase its efficacy and transfusions. If the offending organism is found to be the meningococcus, the appropriate antiserum is administered intravenously. Unfortunately, no effective therapy has as yet been devised. The course is universally rapidly fatal despite treatment.

REPORT OF CASE

On April 14, 1940, L. T., an 18 month old white boy, was brought to the emergency room of the Norwegian Lutheran Deaconesses' Home and Hospital, where he died in a few minutes.

The father stated that the child had been ill on April 1 with an infection of the upper respiratory tract, for which he had been treated by an ambulance

Fig. 1.—Appearance of patient after death.

surgeon and from which he had recuperated in about one week. He was apparently well until the afternoon prior to admission, when he seemed to feel warmer than usual and to be tired. About midnight his parents called an ambulance.

After careful examination for evidence of the exanthems and for neurologic signs, a diagnosis of infection of the upper respiratory tract was again made, and the medicament previously prescribed was readvised. He was given a dose at about 3 a. m. About 4 a. m. the father noticed that discrete hemorrhagic spots were appearing over the child's face and extremities. These lesions rapidly increased in number and size and spread so that by 9 a. m. the eruption had attained massive proportions and widespread distribution. The ambulance was called again, and the child was brought to the emergency room. He died before a complete physical examination could be performed.

His temperature, taken at home, had been 103 F. No neurologic signs could be elicited. There had been no nausea, vomiting or diarrhea. The skin over the entire body was purpuric. There were numerous petechiae in both conjunctivas.

Autopsy.—The body was that of an 18 month old white boy. An extensive purpuric eruption was present on the face, the extremities and the buttocks. The body showed evidence of good nutrition, and there were no signs of external injury. Rigor mortis had set in.

A median incision was made, the sternum was removed and the body cavities were opened.

Thoracic Cavity: The thoracic viscera occupied their normal positions. There was no free pleural fluid. The thymus was somewhat widened and thicker than usual.

Abdominal Cavity: The viscera occupied their usual positions. There was no free peritoneal fluid. There was hemorrhage in the region of the adrenals which was visible through the peritoneum.

Fig. 2.—Extensive purpuric eruption on the trunk and lower extremities.

Cardiovascular System: The heart had stopped in systole. It lay suspended in approximately 4 cc. of clear, straw-colored pericardial fluid. The pericardium was free from any petechial hemorrhages. There was no evidence of gross pathologic change in the heart or the great vessels.

Respiratory System: The tracheobronchial tree was removed at the level of the larynx. No foreign bodies or obstructive processes were found. The lung bed showed no evidence of pathologic changes.

Gastrointestinal Tract and Accessory Organs: These structures showed no abnormalities other than enlargement of the mesenteric nodes, the vermiform appendix and Peyer's patches in the ileum.

Genitourinary Tract: The kidneys still showed some evidence of fetal lobulation. The architecture was essentially normal and well preserved. They emptied via patent ureters into a bladder which contained about 20 cc. of clear urine. There was extensive adrenal cortical hemorrhage, which was limited by the

capsules of the glands but was extensive enough to compress the adrenal tissue markedly.

Genitalia: The genitalia were infantile. The prepuce and the mucosa of the glans penis were purpuric.

Head: There were no deformities. The sutures and the fontanels were closed. The calvarium was removed intact.

Brain: The surface of the cerebrum presented the usual pattern of convolutions, which were deep and well defined. The pia-arachnoid was clearly transparent. No accumulations of purulent exudate were noted. The ventricular system was not dilated, and there was no evidence of neoplasm or obstruction. The cerebellum and the midbrain appeared normal. There was no evidence of fracture or of hematoma of the base of the skull.

Pathologic Observations: There were extensive purpura of the face, the trunk and the extremities, bilateral massive adrenal hemorrhage and hyperplasia of the thymus, the mesenteric lymph nodes, the appendix and Peyer's patches.

Laboratory Data.—Examination of the cerebrospinal fluid (obtained post mortem) showed 450 lymphocytes per cubic millimeter, a negative reaction to the

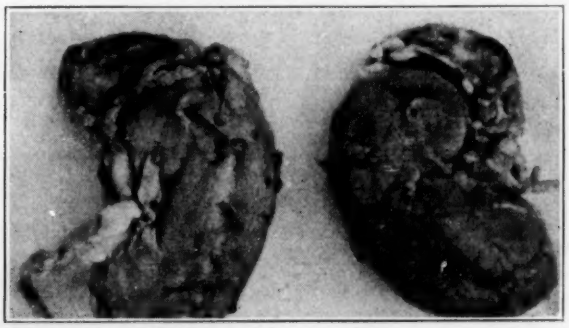

Fig. 3.—Adrenal glands, showing massive hemorrhage.

Benedict test for dextrose and a slightly increased globulin content. By culture a mixture of gram-positive bacilli, diplococci, streptococci and staphylococci was recovered from the fluid.

Culture of blood obtained post mortem yielded no growth until the third day, when a rather sparse growth of staphylococci appeared.

COMMENT

This case demonstrates some of the difficulties encountered in making a diagnosis of the syndrome. In retrospect it is relatively simple to point out that the course was rather characteristic and that the physical signs were rather typical, but it is again emphasized that the cutaneous lesions did not begin to appear until 3 a. m. and that the patient died at 9: 30 a. m. of the same day. As in this case, prior to the appearance of the cutaneous lesions the disease is characterized by a lack of clinical signs.

The results of the cultures of blood and cerebrospinal fluid were more confusing than helpful. Specimens of both fluids were obtained post

mortem, a procedure which has received much criticism from students of bacteriology because its results are unreliable and subject to numerous sources of error. The bacteriologic studies cited in the first part of this paper were for the most part conducted on the living patient; hence, the results are reliable.

The terrifyingly speedy course of this disease gives little opportunity for experimental therapeutics. However, if more clinicians can be informed about it, perhaps the opportunity will arise of trying one or more of the newer chemotherapeutic agents, more particularly sulfanilamide. It seems that this drug should be effective in view of the successful clinical experience with it in meningococcic and streptococcic infections. Early and intensive therapy of this nature is certainly worth trying in a disease with such a universally fatal prognosis.

SUMMARY

A brief historic note and the salient clinical and laboratory features of the Waterhouse-Friderichsen syndrome are presented. In addition, another case is added to the literature, together with the report of the autopsy performed. It is suggested that the newer chemotherapeutic agents be given an opportunity to demonstrate their effectiveness in such cases. In order to do this, however, the possibility that this malady is present must be entertained when an attempt is being made to diagnose an unusual fulminant bacterial infection. It is with the hope that it may serve to emphasize and fix the clinical characteristics of the Waterhouse-Friderichsen syndrome that this paper is submitted.

TULAREMIA WITH EXTENSIVE PHARYNGITIS

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In the typical case of tularemia there is an ulcer on the surface of the body or an inflammation of the conjunctiva, lesions which indicate the point of entry of the infecting organism. In a rare case such usual superficial lesions are absent and the exact method of dissemination remains obscure. The present report is concerned with a case in which the preponderance of evidence indicates that Bacterium tularense entered through the mucosa of the pharynx.

REPORT OF A CASE

The patient, a 7 year old white boy who lived in a rural Illinois community, entered the St. Louis Children's Hospital on Dec. 1, 1939. The present illness had begun three days previously, when he complained of fever, sore throat and pain in his head and back. At the time of entry to the hospital, no family or personal history of significance was obtained except that for several years the child had had occasional convulsions of the right side of his body, which had been diagnosed as manifestations of jacksonian epilepsy with cortical degeneration of the left cerebral hemisphere.

Physical Examination.—When examined in the hospital the boy appeared extremely ill and poorly nourished. His wrists were held flexed, and his right foot was held in equinovarus position. The most conspicuous physical sign was an acute, necrotizing inflammation of the pharynx and the tonsils. The oral mucous membrane was red, and the tonsillar surfaces were dotted with a fine gray exudate.

Course.—In the hospital the inflammatory process progressed until the entire pharynx, including the tonsillar pillars, the adjacent portion of the mucosa of the mouth and the tongue, were covered by a thin gray membrane. This could be removed with ease, to disclose a necrotic base. The entire pharyngeal wall was swollen, and the cervical lymph nodes were palpable. Respiratory difficulty due to the presence of purulent mucus in the trachea was relieved temporarily by tracheotomy on December 5. However, two days later the enlargement of the cervical nodes had become more marked and the respiratory passages were again filled with exudate. In order to remove the exudate a bronchoscope was passed. The mucosal surfaces of the trachea and the large bronchi were seen to be inflamed. Sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) was administered first, and a concentration of 12.5 mg. of the drug per hundred cubic centimeters of blood was obtained; however, sulfanilamide was substituted when cultures of material from the throat yielded hemolytic and nonhemolytic streptococci. This therapy had no apparent effect on the course of the disease. Diphtheria antitoxin was also given because the appearance of the throat sug-

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gested a diphtheritic membrane. Repeated blood cultures were sterile, and the spinal fluid was normal. The child's temperature throughout his illness fluctuated in the neighborhood of 104 F. The respiratory difficulty increased, and the patient died on December 9, twelve days after the onset of the illness.

Autopsy.—The autopsy was performed by Dr. Gerald Slusser.

Gross Examination: There was marked bilateral enlargement of the cervical lymph nodes, but no other superficial nodes were enlarged. The edges of the tracheotomy wound were necrotic; the body cavities contained no free fluid and had smooth serous linings. On the hyperemic, edematous mucosal surface of the trachea were small, irregular areas covered with yellow fibrinous exudate. The pleural surfaces of the lungs were smooth and mottled with dark reddish purple areas. On section the parenchyma of both lungs showed gray and dark red mottling and had a granular appearance, more marked in the left lung. The liver was enlarged, weighing 780 Gm. There were many small yellow foci, varying from 0.5 to 2 mm. in diameter, on the capsular surface, and section showed similar lesions evenly distributed throughout the organ. The spleen was enlarged and firm, weighing 150 Gm. The cut surface was studded with small yellow nodules similar to those in the liver. The intestinal tract showed no abnormalities except a small mucosal polyp in the transverse colon. The lymph nodes, other than those in the cervical region, were not unusually large. The left cerebral hemisphere was smaller than the right but showed no evidence of a recent pathologic process.

Microscopic Examination: The tracheal mucosa was entirely replaced by a large mass of fibrin, in which dark-staining bacterial colonies and many necrotic mononuclear and some polymorphonuclear cells were enmeshed. This infiltration extended down around normal glands and cartilages. Many of the pulmonary alveoli contained fibrin and irregular areas of cellular infiltration, which were most prominent about small bronchi. These infiltrations were composed of large mononuclear cells with large vesicular nuclei and dark eosinophilic cytoplasm, small mononuclear cells with dark-staining, indented nuclei surrounded by blue cytoplasm and a smaller number of polymorphonuclear leukocytes. Many of the bronchi contained homogeneous material which stained red and blue and in which were enmeshed a few cells similar to those in the infiltrations. In the liver there were focal areas of necrosis, which showed fragmented hepatic cells and dilated sinusoids, with only occasional groups of two or three normal-appearing parenchymal cells. There was moderate infiltration with cells similar to those seen in the lung. The necrotic foci in the spleen were composed of infiltrations of the same types of cells as those in the lung and liver. There were also areas of widely dilated sinusoids which contained the outlines of many red blood cells.

Bacteriologic Studies.—Cultures of blood obtained from the heart at autopsy contained Staphylococcus albus, and those of material taken from the lungs and the trachea contained Staphylococcus aureus. Because on both gross and microscopic examination the lesions suggested a diagnosis of tularemia, the following bacteriologic studies were carried out: A small portion of the spleen was ground up and injected subcutaneously into a guinea pig; another portion of the splenic emulsion was rubbed into the skin of the shaved abdomen of a second guinea pig. The first animal died four days and the second six days after these procedures were carried out. The spleen and the liver of both contained lesions which were grossly and microscopically characteristic of tularemia. Material from these animals was cultured on cystine-blood agar plates, and in a few days several small colonies of minute, gram-negative coccobacilli appeared, but not in sufficient numbers for agglutination tests.

Additional History and Serologic Studies.—After obtaining the foregoing evidence of tularemia, the following additional history was obtained from the patient's family. On November 19 and November 23, nine and five days before the onset of the patient's illness, the family had eaten rabbits, which had been killed and cleaned by members of the immediate family and relatives. Although it could not be ascertained whether the patient had eaten this meat, he was present when the rabbits were cleaned and prepared for cooking. In 2 relatives who had helped to clean the rabbits typical ulceroglandular tularemia developed on November 21, and on November 23 a third relative had severe sore throat accompanied by enlargement of the cervical lymph nodes, chills, aches and pains. Blood taken on December 30 from the latter relative and from 1 of the 2 with ulceroglandular tularemia agglutinated Bact. tularense in dilutions of 1 to 2,560. In a fourth relative, 18 months of age, fever, sore throat and pain in the chest developed on November 26. A sample of his blood, obtained on December 30, also agglutinated Bact. tularense in a dilution of 1 to 2,560. All 4 of the patient's relatives with tularemia recovered.

Comment on the Case.—The patient was admitted to the hospital during a mild epidemic of laryngotracheobronchitis. During a period of approximately two months 24 patients with this disease were admitted to the hospital. The patients with the most severe form of the disease required tracheotomy, with subsequent tracheal suction and bronchoscopic removal of the secretion which obstructed the bronchi. The causative organism was frequently the hemolytic streptococcus but occasionally was the pneumococcus or the staphylococcus. Response to chemotherapy was striking in those cases in which the pneumococcus and the hemolytic streptococcus were the infecting organisms. The disease in the case of this boy seemed to be similar to that in the other cases, and the only discordant note was the lack of improvement with chemotherapy, which was instituted after hemolytic streptococci were isolated from material from the throat.

COMMENT

The microscopic lesions in the liver, the spleen and the lungs in the case reported are similar to those described in other cases of tularemia and deserve no special mention. However, the occurrence of necrotizing pharyngitis, such as was present in this case, has been reported but rarely. It is of special interest because no other superficial ulcerative lesion was found to indicate the point of entry of the organisms into the body. The absence of other lesions and the involvement of the regional lymph nodes make it seem likely that the infective agent entered the body by the oral route. It is interesting that 2 of the patient's relatives who also contracted tularemia likewise gave a history of sore throat without other superficial lesions.

Only 3 other instances of ulcerative pharyngitis occurring in a case of tularemia have been reported in the literature. One case, reported by McGovern,[1] was that of a white woman 32 years of age who had picked ticks from her dog. She had a "large confluent ulceration involving

1. McGovern, F. H.: Primary Tularemic Ulcers in Pharynx, J. A. M. A. **107**:1629 (Nov. 14) 1936.

almost the entire right side of the posterior wall of the pharynx; many discrete shallow ulcerations, measuring from 2 to 3 cm. in diameter, covered with a gray exudate, were scattered over the posterior pharyngeal wall. The cervical glands were bilaterally enlarged and tender." This patient recovered after an illness of two months. Another case, reported by Pessin,[2] was that of a white woman 55 years of age who had small, grayish red ulcers on the dorsum of the tongue, with dirty gray accumulations at the alveolar borders and other small gray ulcers on the mucosal surface of the right cheek. This patient died as the result of pericarditis and pneumonia. In neither of these cases was there any other lesion which could be considered the initial lesion of tularemia.

In a third case, reported by Bernstein,[3] there was stomatitis which was probably due to tularemia. On the right thumb of this patient, a white man aged 52, a fissured ulcer developed after he had skinned a wild rabbit. He had "no palpable glands save in the left cervical chain. His tongue was very red and deeply fissured. There were patches of grayish exudate with a hemorrhagic base on the soft palate."

These 3 cases and the one reported in this paper have several things in common. The lesions of the mouth and pharynx were described as ulcerations covered with a gray exudate. These ulcerations varied in size from those described as small to those which included all or a large part of the pharyngeal wall. In every instance, except 1 in which no mention was made of the cervical nodes, enlargement of the cervical nodes was associated with the pharyngeal ulcerations. The difficulty in making a differential diagnosis and the confusion of the clinical picture with that of a diphtheritic or streptococcic pharyngitis make the case reported in this paper of particular interest, both clinically and pathologically.

SUMMARY

The case of a 7 year old boy with tularemia is reported in which the chief clinical manifestation of the disease was a necrotizing ulceration of the entire pharyngeal wall, extending to the surface of the tongue and to the oral mucosa. Reference is made to 3 other reported cases in which similar lesions were found. In only 1 of these was there a cutaneous lesion. Although no final decision can be reached as to the mode of entry of the organism into the body in the present case, the absence of other superficial lesions makes ingestion of the infective material the most probable route of infection.

Dr. Margaret G. Smith and Dr. Henry Allen carried out the bacteriologic and serologic studies in this case, and Dr. Alexis Hartmann supplied the clinical data.

2. Pessin, S. B.: Tularemic Pneumonia, Pericarditis and Ulcerative Stomatitis, Arch. Int. Med. **57**:1125 (June) 1936.

3. Bernstein, A.: Tularemia, Arch. Int. Med. **56**:1117 (Dec.) 1935.

AURICULOVENTRICULAR (NODAL) RHYTHM IN ACUTE RHEUMATIC FEVER

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Nodal rhythm is one of the less common disorders of the cardiac mechanism. It may occur as a functional disturbance secondary to altered vagal tone and as such may appear after the administration of digitalis or atropine. It is occasionally encountered in arteriosclerotic heart disease, and a few authors have reported its occurrence in acute rheumatic fever. In 1937 Cutts [1] reported 12 cases of interference dissociation, a variety of nodal rhythm, of which 6 were associated with acute rheumatic fever and 1 with tonsillitis. He stated that reports in English on nodal rhythm and interference dissociation have not mentioned rheumatic fever as an important cause. McMillan and Cook [2] reported 2 cases of nodal rhythm occurring in the course of rheumatic fever, in 1 of which, however, digitalis had been administered. Bain [3] described the case of a patient suffering from rheumatic fever who exhibited auricular fibrillation, reciprocal rhythm, nodal rhythm and partial heart block before normal rhythm was resumed. Oettinger and Neslin [4] found 14 examples of nodal rhythm among 200 cases of rheumatic fever in which electrocardiographic studies were made. They observed that the nodal rhythm persisted for one to six days. Small doses of atropine increased the rate of each pacemaker, while larger doses restored the sinus rhythm. Most recent writers on this subject have passed over the earlier and important communication of Cowan, Fleming and Kennedy.[5] These observers reported in detail 7 cases of

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1. Cutts, F. B.: The Transitions Between Normal Sinus Rhythm, Ventricular Escape, A-V Nodal Rhythm, and A-V Dissociation, Am. Heart J. **13**:451, 1937.

2. McMillan, T. M., and Cook, A.: Electrocardiographic Changes Occurring During Rheumatic Fever, Atlantic M. J. **31**:806, 1927.

3. Bain, C. W. C.: Interference Dissociation, Lancet **1**:20, 1939.

4. Oettinger, I., and Neslin, W.: Über atrioventrikuläre Automatie bei rheumatischer Karditis, Deutsches Arch. f. klin. Med. **173**:212, 1932.

5. Cowan, J.; Fleming, G. B., and Kennedy, A. M.: Nodal Rhythm and Heart Block in the Acute Infections, Tr. Internat. Cong. Med. (1913), 1914, sect. 6, pt. 2, p. 223.

nodal rhythm in which polygraphic tracings showed close conjunction of the auricular and the ventricular contractions. In 1 the patient recovered. In 6 cases the heart was studied, and histologic examination revealed inflammatory reaction within the auriculoventricular node in each.

At present, electrocardiographic examination probably represents the most valuable laboratory procedure available for the diagnosis of acute rheumatic fever. It is said that if frequent examinations are made disorders of the cardiac mechanism will be found in approximately 90 per cent of cases of the acute form. The majority of such disturbances represent conduction defects, commonly, partial auriculoventricular block. It is now known that these conduction disorders may usually be relieved, temporarily or permanently, by atropine (Bruenn,[6] Wedd [7]). This relates them to the chemical rather than to the cellular pathologic changes of acute rheumatic fever. Inasmuch as the action of the vagus nerve or a cholinergic toxin on the auriculoventricular node is at least qualitatively similar to their action on the sinus node, the genesis of nodal rhythm is obviously different from that of the conduction disturbances. The appearance of nodal rhythm in these cases is dependent on raised automaticity of that node, and this in turn may be determined by the presence of actual inflammatory processes within the node, as Cowan has demonstrated.

Because the association and significance of nodal rhythm with acute rheumatic fever do not seem to be widely recognized, the following case is presented.

REPORT OF A CASE

History.—Eugene B., an 8 year old white boy, who was referred by Dr. Walter Allen, was admitted to Strong Memorial Hospital on March 2, 1940, with the complaint of pains in his "stomach" and joints of two days' duration. About two months earlier he had had a sore throat, but he had been in good health since until three days before admission, when he was found to have slight fever. The following morning he awoke with pain in his abdomen, which was not relieved by an effectual cathartic. The next day the boy complained of painful ankles and knees. He was known to have had a sore throat on several previous occasions, but otherwise his past history was irrelevant. Little was known of the family history.

Physical Examination.—When the patient was admitted to the hospital the temperature was 40 C. (104 F.), and the pulse rate was 125 and the respiratory rate 34 per minute. He was a slender, well developed boy, who appeared moderately ill. The skin was hot and dry. The tonsils had been removed, but the pharynx showed considerable injection. There was slight pain on flexion of the neck.

6. Bruenn, H. G.: The Mechanism of Impaired Auriculo-Ventricular Conduction in Acute Rheumatic Fever, Am. Heart J. **13**:413, 1937.

7. Wedd, A. M.: Complete Heart Block in Acute Rheumatic Fever, Am. Heart J. **14**:759, 1937.

The lungs appeared clear on percussion and auscultation. The heart seemed to be of normal size. A soft blowing systolic murmur was heard at the apex. Both ankles were slightly swollen and tender, with erythema of the overlying skin. Other results of the examination were normal.

Laboratory Data.—A blood count showed 3,870,000 erythrocytes and 18,000 white cells, of which 83 per cent were polymorphonuclear leukocytes, 12 per cent lymphocytes and 5 per cent monocytes. The blood smear showed no abnormalities. The hemoglobin content was 12.5 Gm. per hundred cubic centimeters of blood. The Wassermann reaction of the blood was negative, and a culture of the blood showed no growth. Dick and Schick tests and a Mantoux test with human old tuberculin (1 : 1,000 dilution) gave negative results. Examinations of the feces and the urine showed nothing abnormal. From a culture of material from the pharynx a beta hemolytic streptococcus was obtained, and the patient's plasma showed a marked increase in resistance to lysis by a fibrinolytic strain of beta hemolytic streptococcus. The sedimentation rate was 1.9 mm. per minute (0.35 mm. per minute is the upper limit of normal for the method used). Roentgen examination of the chest showed the heart to be of normal size and shape. The electrocardiograms will be discussed later.

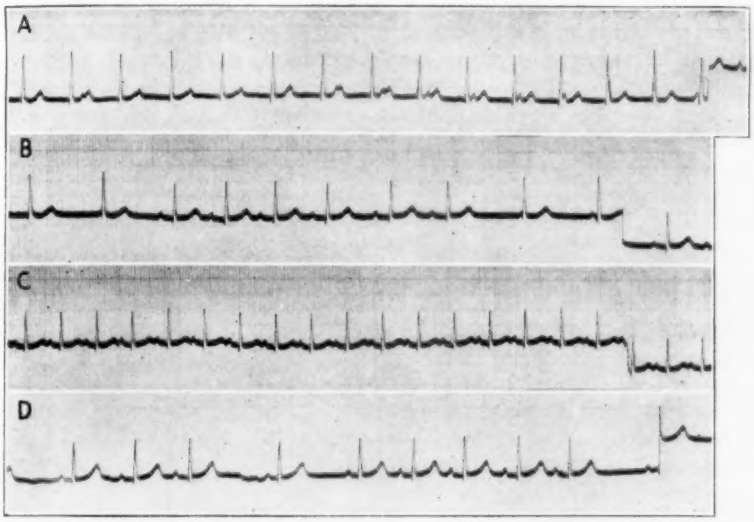
Course in the Hospital.—The boy was kept in bed and given small doses of phenobarbital. The pain and tenderness in the ankles did not seem sufficiently severe to warrant the use of salicylates. All symptoms disappeared within a few days, and by the end of the first week the temperature and the pulse and respiratory rates were within normal limits. The sedimentation rate decreased gradually and was 0.3 mm. per minute four weeks after the onset of symptoms. However, in spite of the apparently mild course in the hospital a diastolic murmur, which was best heard at the left sternal border at the level of the third and fourth interspaces, developed and was thought to indicate an early stage of aortic insufficiency. The blood pressure was then 100 mm. of mercury systolic and 65 mm. diastolic. Pulsation in the peripheral vessels was of normal character. The patient was discharged on April 11. The final diagnosis was acute rheumatic fever and rheumatic heart disease with aortic insufficiency.

Electrocardiographic Examinations.—The electrocardiogram taken on the day of admission is reproduced in *A* of the figure. From this record it is seen that the auricles and the ventricles were beating independently. The auricular rate was 92 and the ventricular 90 per minute. Unfortunately, only three short tracings were sent from the laboratory; in these no instance of ventricular response to an auricular beat was seen. The interpretation of such records is not always simple. Had a longer record been available one might have seen that there was an occasional ventricular response to an auricular beat, which would have identified the arrhythmia as one of interference dissociation. Nevertheless, we believe this to be an example of the type II nodal rhythm described by Mobitz [8] and not one of auriculoventricular dissociation with a rapid idioventricular rhythm. In the past, as Mobitz pointed out, similar high ventricular rates have been erroneously attributed to a rapid idioventricular rhythm. In 1934 Pomerance and Frucht,[9] in their paper on heart block in rheumatic fever, reported 2 cases of dissociation,

8. Mobitz, W.: Zur Frage der atrioventrikulären Automatie. Die Interferenzdissoziation, Deutsches Arch. f. klin. Med. **141**:257, 1923.

9. Pomerance, M., and Frucht, S.: Heart Block in Rheumatic Fever, Am. J. Dis. Child. **47**:1087 (May) 1934.

in 1 of which the ventricular rate was 80 and in the other 120 per minute, which they called complete block. Their case 2 may well have been one of nodal rhythm, and case 3 almost certainly was one of interference dissociation. However, it must be admitted that the differentiation of nodal from idioventricular rhythm may not always be possible. While the dictum of Mobitz—that if the ventricular rhythm in questionable cases has a frequency of more than 50 beats per minute that rhythm comes from the auriculoventricular node and not from tertiary centers—usually holds true, and certainly in most instances of unquestioned idioventricular rhythm the rate rarely exceeds 40 per minute, that rule may not necessarily hold when idioventricular rhythm appears during acute infections. In 1932 Wedd [10] reported a case of acute rheumatic fever in which there was first shown a regular ventricular rhythm with a rate of 68 per minute, which was attributed to complete heart block, and in all probability correctly, for in that



Electrocardiograms taken *A*, March 4, 1940; *B*, March 6; *C*, March 6, after administration of atropine sulfate, and *D*, March 11.

instance the auricles were fibrillating. On the second day the ventricular rhythm was totally irregular and its rate was 110 per minute.

Confirmation of the diagnosis of nodal rhythm in the case under consideration is seen in the record obtained two days later (*B* of the figure), which shows two pairs of nodal beats separated by a period of sinus rhythm. The irritability of the auriculoventricular node was then decreasing, but it still asserted itself after a period of sinus slowing. In subsequent records no nodal beats were observed. In many examples of this type of nodal rhythm the frequency of the auriculoventricular node is higher than that of the sinus. When the frequencies are

10. Wedd, A. M.: Complete Heart Block, Auricular Fibrillation and Abnormal Ventricular Complexes in a Case of Acute Rheumatic Fever: Partial Heart Block in Acute Rheumatic Fever, Clifton M. Bull. **18**:63, 1932.

separated by a considerable interval, interference dissociation is favored. In our case the two frequencies were so close that sinus impulses found the node refractory when they reached it. It is also possible that because of the nature of the underlying lesion the stimuli arising in the auriculoventricular node were of greater intensity than those of the sinus node, and this was a factor in the temporary domination of the ventricle by the auriculoventricular node.

After the intramuscular administration of 0.8 mg. of atropine sulfate the nodal rhythm was replaced by a normal sinus rhythm with a rate of 127 per minute and a PR interval of 0.16 second (*C* of the figure). Reduction (by atropine) of vagal tone at the sinus node raised its rhythmicity well above that of the lower node and thus permitted the sinus to resume its normal role of pacemaker.

In the present case disturbance in aurciuloventricular conduction was not marked. In *D* of the figure it is seen that there was sinus arrhythmia, rate 70 per minute, with PR intervals varying from 0.16 to 0.21 second. An electrocardiogram taken on March 15 showed a rate of 88 per minute, with an average conduction time of 0.16 second; the range was from 0.13 to 0.18 second, and no interval in that or in subsequent records taken during the period of observation exceeded 0.20 second.

Attention may be called to the sinus arrhythmia demonstrated in *D* of the figure. Sir James Mackenzie [11] emphasized the favorable aspect of this arrhythmia in rheumatic heart disease. But in doing so he referred to its appearance after fever, tachycardia and signs of active infection had disappeared. For him it represented the return of the "youthful irregularity" normal to childhood. In 1921, in a consideration of the occurrence of sinus arrhythmia in obviously diseased hearts, Wedd [12] suggested that there might be times in the course of rheumatic fever when sinus arrhythmia could be interpreted as an expression of myocardial irritation. Its presence in this case when there were clinical signs of activity and simultaneous with periods of nodal rhythm and prolonged conduction indicates that it is probably similar in nature to those disturbances and has the same significance. This view does not in any way negate the teaching of Mackenzie concerning the later appearance of the arrhythmia when the infectious process has subsided. The evaluation of sinus arrhythmia in this disease should be made in the light of other factors present at the time it appears.

SUMMARY

An example of transient auriculoventricular rhythm, which occurred early in the course of acute rheumatic fever is described. After administration of atropine the sinus node controlled the ventricle. The genesis of nodal rhythm, in contrast to conduction disturbances, is considered, and the significance of some of the disorders of the cardiac mechanism encountered in the course of acute rheumatism is discussed briefly.

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11. Mackenzie, J.: Diseases of the Heart, ed. 4, London, Oxford University Press, 1925, p. 123.

12. Wedd, A. M.: Neurogenic Irregularities of the Heart in Adults, Am. J. M. Sc. **162**:49, 1921.

Progress in Pediatrics

MEDALLIONS AND PLAQUES OF INTEREST TO PEDIATRICIANS

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CHICAGO

Commemorative medallions are metal tokens struck in honor of a living or a dead person or in celebration of a great event. Few duplicacates are made, a custom which accounts for the rarity of these art treasures.

A likeness of a man so honored appears usually in bas-relief on the obverse (the face) of the medallion; the dates of his birth and death and a descriptive phrase to explain his claim to fame are usually given on the reverse. Occasionally the latter side also bears an allegoric figure, symbolizing his work.

In spite of the rarity of medical medallions, I have been able to collect during my travels a sufficient number to get a bird's-eye view of medical history. Among them are a few of special interest to pediatricians. One cannot, of course, expect medallions of pediatricians in large numbers, since pediatrics as a specialty is less than a hundred years old. I know of only two medallions of pediatricians in the modern sense of the term, those of Jacobi and of Pirquet. There are, however, a few medallions of men who lived more than a century ago, yet made contributions to pediatrics. Also, several events of special interest to pediatricians have been thus commemorated.

FRIEDRICH HOFFMANN

Friedrich Hoffmann (1660-1742) was a pupil of Hermann Boerhaave, the Dutch clinician, who counted among his pupils leading physicians of the latter part of the seventeenth century and the early part of the eighteenth century.

Hoffmann's chief contribution to pediatrics was his description of German measles; of less imporance was his study of scrofula. To the laity he was known through Hoffmann's anodyne (compound spirit of ether), which was popular for many years. There are two medallions of him. The one in my collection is part of the Numismatic Series of Illustrious Men and was struck in 1823. The reverse gives the dates of his birth and death (fig. 1).

NICHOLAS ROSEN VON ROSENSTEIN

Nicholas Rosen von Rosenstein (1706-1773) has deservedly been called a great pioneer in pediatrics. A pupil of Boerhaave and a contemporary of Linnaeus, he received recognition in his own country, Sweden, and abroad. He wrote a monograph on scarlet fever and one on tuberculosis and was among the first physicians to deal with the question of milk dilution for infants. There were two medallions of

Fig. 1.—Medallion of Friedrich Hoffmann. *A*, obverse; *B*, reverse.

Fig. 2.—Medallion of Nicholas Rosen von Rosenstein. *A*, obverse; *B*, reverse.

him, both rare now. A duplicate of the one in my possession is in the cathedral of Uppsala, where Rosen von Rosenstein is buried (fig. 2).

BENJAMIN RUSH

Benjamin Rush (1743-1813) described epidemics of yellow fever, influenza and measles. Of special significance was his paper entitled "An Inquiry into the Cause and Cure of Cholera Infantum" (1773). Cholera infantum had previously been ascribed to dentition, to worms and to the eating of fruit during the hot summer. Rush refuted all these ideas, and advanced the opinion that cholera in infants was similar to

cholera in adults, although he did not state the cause of the disease in the latter. Rush's treatment of cholera infantum is interesting, but even more so is his advice on prevention:

1. The daily use of the bath.

2. A faithful and attentive accommodation of the dresses of children to the state and changes of the air.

3. A moderate quantity of salted meat taken occasionally in those months in which the disease usually prevails. It is perhaps in part from the daily use of salted meat in the diet, that the children of country people escape this disease.

4. The use of sound old wine in the summer months. From a teaspoonful, to half a wineglass full, according to the age of the child, may be given every day. It is remarkable that children of persons in easy circumstances, who sip occasionally with their parents the remains a glass of wine after dinner are much less subject to this disease, than the children of poor people, who are without the benefit of that article of diet.

Fig. 3.—Medallion of Benjamin Rush.

5. Cleanliness, both with respect to the skin and clothing of children. Perhaps the neglect of this direction may be another reason why the children of the poor are most subject to this disease.

6. The removal of children into the country before the approach of warm weather. This advice is particularly necessary during the whole period of dentition. I have never known but one instance of a child being affected by this disease, who had been carried into the country in order to avoid it.

The medallion has on the obverse a likeness of Rush, with the hairdress characteristic of his day, and an inscription: Benjamin Rush M:D: of Philadelphia (fig. 3). On the reverse is the date, MDCCCVIII.

EDWARD JENNER

Edward Jenner (1749-1823) not only saved thousands of adults and children from the scourge of smallpox through his discovery of vaccination, but opened up an entirely new field of study, from which originated the branch of medicine later known as immunology. Jenner announced

his belief in the effectiveness of cowpox as an immunizing agent after years of observation of the immunity developed in dairymaids and servants who had been infected with cowpox. In May 1796 Jenner transferred matter from the hand of a young woman who was infected with cowpox into the arm of an 8 year old boy. Six weeks later he introduced matter from a smallpox pustule into the boy's arm, but smallpox did not develop. This was one of the most daring and crucial experiments in medicine.

Several medallions of Jenner have been struck. Most of them have the likeness of a cow on the reverse.

CHRISTOPH WILHELM HUFELAND

The popularization of vaccination in Germany was due to the work of Christoph Wilhelm Hufeland (1762-1836). In addition, Hufeland

Fig. 4.—Medallion of Christoph Wilhelm Hufeland. *A*, obverse; *B*, reverse.

wrote on school hygiene and on scrofula. Two medallions were struck in his honor. The one in my possession has the head of Hufeland and his name on the obverse. On the reverse are a monument, the staff of Aesculapius and a parchment, before which a nude angel offers a drink to a half-nude woman with two infants. Another nude angel extends the thread of life (fig. 4).

CHARLES MICHEL BILLARD

Like the French anatomist Bichat, who in the short span of thirty-one years accomplished so much for medicine, Charles Michel Billard (1800-1832) made a great contribution to pathology and pediatrics in only thirty-two years of life. Billard's two main achievements were the correlation of clinical data with postmortem changes and his book on the newborn, which contains a wealth of interesting observations. He emphasized the importance of careful examination of babies. He devoted one chapter to the discussion of the pulse and its modifications, a few chapters to a description of the skin of newborn infants and a great deal

of space to the significance of the cry in infancy. Of particular interest are his views on cerebral pathologic conditions of newborn infants and on gastrointestinal disturbances in babies. He expressed the belief that passive congestion of the cerebrospinal apparatus is common at birth and attributed its occurrence to the abundance of vessels, the slowness of circulation and the influence of respiration on the spinal and the cerebral circulation. As to gastrointestinal disturbances, he has this to say:

> There are a great number of children affected with diarrhea without enteritis; they become pale and sink into a state of marasmus, and on examining the dead body no trace of inflammation will be found in the intestine.

Fig. 5.—Placque of Charles Michel Billard, by David d'Angers.

In 1828, the same year in which Billard published his book on the disease of the nursling, he published an atlas of pathologic anatomy of childhood, illustrated with ten plates.

A plaque of Billard (fig. 5) was made by the famous medallionist David d'Angers, his countryman and friend, the same artist who struck the Magendie plaque.

JUSTUS VON LIEBIG

Justus von Liebig (1803-1873), a chemist, left his imprint on pediatrics through the malt soup he prepared. Liebig's malt soup was a pediatric standby during the last generation. The medallion in his honor was struck in 1903.

ODILON MARC LANNELONGUE

Odilon Marc Lannelongue (1841-1911) was one of the few early pediatric surgeons. Two medallions were struck in his honor. On the obverse of the one in my possession appears his head, his name, his title and the inscription *Ses élèves—ses amis* (from his pupils and his friends). On the reverse a woman, apparently representing surgery, is about to trephine the skull of an infant in its mother's arms. At one side is a man with his arm in a sling. Above is a shelf with pharmaceutic jars. The inscription is *Mentis manusque per opus* (through the work of the mind and the hand).

ADOLPHE PINARD

Adolphe Pinard (1844-1934) was an obstetrician whose claim to pediatric fame is based on his advocacy of maternal nursing. There is only one medallion of Pinard (fig. 6). His head appears on the obverse while on the reverse is shown a mother and child, with the inscription *Le lait de la mère appartient a l'enfant* (the milk of the mother belongs to the child). In addition, the notation *XX ans de professorat à la maison Baudelocque* (twenty years of professorship in the Baudelocque hospital) is accompanied by a crude reproduction of that institution. This medallion was issued by the Society for Puericulture (child welfare) of France, in recognition of Pinard's service to children.

EMIL VON BEHRING

Emil von Behring (1854-1917) announced the preparation of diphtheria antitoxin in 1890, a discovery that has saved the lives of thousands of children. In 1915 he reported on the efficacy of toxin-antitoxin for the prophylaxis of diphtheria, a suggestion originally made by Theobald Smith, in 1907. There is only one plaque of von Behring (fig. 7), made in 1915. On the obverse is his likeness, with the staff of Aesculapius beneath it and the inscription *Emil von Behring: Seines Alters 61 Jahre.*

On the reverse is an inscription around the edge, *25 Jahre Serum Therapie. 4 Dez., 1890—4 Dez., 1915.* A human figure is shown chasing death away from a cradle. The pewter plaque was given to me by the Chemical Dye Works, in Germany, the first manufacturer of antitoxin. The plaque is signed by Kraumann.

ABRAHAM JACOBI

Abraham Jacobi (1830-1919) did more than any other single person in establishing pediatrics as a specialty. The first professor of pediatrics in this country, he also founded and assisted in the publication of more than one pediatric journal.

Jacobi's work on infant feeding was outstanding. He was probably the first physician who realized the significance of boiling milk, which

Fig. 6.—Medallion of Adolphe Pinard. *A*, obverse; *B*, reverse.

Fig. 7.—Placque of Emil von Behring.

practice he advocated persistently. His instructions regarding the care and hygiene of infants are sound.

Like Epstein of Prague, he recognized the fallacy and danger of washing an infant's mouth. Like Epstein, too, he constantly advocated

the use of breast milk and emphasized the fact that cow's milk is never as good as human milk.

Jacobi's work on diphtheria was notable. With no antitoxin at his command, he did the best he could by means of local and internal medication, always, however, avoiding the use of poisonous drugs. When intubation was described by Joseph O'Dwyer, Jacobi was the first physician in the United States to practice it.

Jacobi was connected in some way with nearly every medical institution in New York that lays claim to any work with children. He organized the children's department of Mount Sinai Hospital and was one of the founders of the German Hospital of New York City and the organizer of its children's department.

Fig. 8.—Medallion of Clemens von Pirquet.

No wonder he was known abroad, as well as in this country, as the father of American pediatrics.

The medallion in my possession was struck in 1915. On the obverse is the likeness of Jacobi, with the inscription "May 6, 1830—May 6, 1915." On the reverse is the inscription: "Souvenir and Testimonial Banquet Tendered Dr. A. Jacobi under the Auspices of the Bronx Hospital and Dispensary May 6, 1915."

CLEMENS VON PIRQUET

Clemens von Pirquet (1874-1929), professor of diseases of children at the Universities of Breslau and Vienna, and at one time professor of pediatrics at Johns Hopkins University, is generally known for the cutaneous tuberculin reaction that bears his name. However, he did much more than devise this test. Through his studies of serum sickness

and the stages of vaccination, he discovered the principles of allergy and thus introduced a new concept in medicine and threw light on the pathogenesis of many diseases, such as asthma and eczema. He also described a new system of feeding, known as the nem system, in which he used the sitting height, instead of the weight, as an index of food requirement.

The medallion of Pirquet was struck in 1924 (fig. 8).

VACCINATION

Several medallions commemorate the introduction of vaccination by Jenner. The one in my collection has on the obverse a cow with full udder and a vaccination lancet. Beneath the cow is an inscription, *Ex insperato salus* (fig. 9).

The medallion was struck in 1814 by the municipality of Paris, sixteen years after the publication of Jenner's book, "The Cowpox."

Fig. 9.—Medallion commemorating the discovery of vaccination by Edward Jenner.

CHILD WELFARE

The organization of La Société Protectrice de l'Enfance (society for the protection of children), which had its inception in France in 1865, is commemorated by a medallion which protrays a mother holding one child in her arms and leading another by the hand. It bears the inscription *Alendis parvulis* (for the protection of little ones). This medallion served to bring before the public both the needs and the accomplishments of this society, which investigated the condition of the children of the poor, helped to improve their home conditions, supplied them with milk and, above all, saw to the passing of laws for the protection of young children.

LAW OF ROUSSEL

A medallion was issued by the ministry of the interior of the French Republic to celebrate the passing of a law for the protection of the young. The *loi Roussel* was intended to protect the infants of peasant women, who often neglected their own babies to nurse the infants of the rich. The law made it imperative for wetnurses to obtain certificates from the local mayor to the effect that their own babies were 7 months of age or older.

The law also safeguarded the health of the infants of mothers who worked in factories by provisions for governmental inspection and certification of all places in which children under 2 years of age were farmed out.

This law is commonly held responsible for a reduction in infant mortality in France from 78 to 15 per cent. One French writer asserted that it established the principle that the welfare of the child takes precedence over all other considerations.

The promulgator of this humane law was Théophile Roussel (1816-1903), a French physician who was known as the friend of abandoned children. One of his admirers, on returning from a visit to Roussel's native village, spoke of it as a land in which there were no orphans, for those who had lost their parents had Father Roussel to take care of them. Garrison, in describing the personal magnetism and modesty of Roussel, related that when an important jubilee was held to celebrate Roussel's achievements for the cause of infant welfare, the physician said, with charming simplicity, "It is a celebration for the Society for the Protection of Children (and not for me)."

Roussel was also responsible for the passing of a law for suppression of public drunkenness and for organization of medical charity. "The ruling principle of his life," Garrison stated, "was to translate charitable sentiment into enacted law."

The medallion shows a mother holding one child at her breast while she feeds another with a spoon. She is blowing on the hot food in the spoon, a custom that is not obsolete among mothers even today.

MISCELLANEOUS

There are a number of medallions with child motifs in my possession which are interesting both from an artistic and from a pediatric standpoint.

Correspondence

HERPANGINA

To the Editor:—The interesting article by Dr. B. B. Breese Jr. entitled "Aphthous Pharyngitis" (Am. J. Dis. Child. **61**:669 [April] 1941) impels me to report that this disorder, which I regard as a specific disease, was described by me in two articles entitled "Herpetic Sore Throat" (*South. M. J.* **13**:1871, 1920) and "Herpangina" (*Arch. Pediat.* **41**:181, 1924). Naturally, I am gratified to find that other pediatricians, such as Levine, Hoerr and Allanson (*J. A. M. A.* **112**:2020 [May 20] 1939) and, more recently, Breese, have corroborated my earlier observations.

I suggested the name herpangina for this disease. In this connection I should like to point out that the terms aphthous and herpetic are hopelessly confused in the literature. I have taught in recent years that the word aphthous should be applied to superficial erosions or macular infiltrations of the mouth. The typical aphthous stomatitis occurs in the front of the mouth in the form of macular lesions —superficial erosions and fibrinous subepithelial deposits. Bedner's aphthae also suggest such a lesion on the palate. Some forms of ulcerative stomatitis may also be designated as aphthous, since they are characterized by erosion.

The term herpetic stomatitis should be used for a condition in which the lesions are vesicular or when observed are deep punched-out ulcers, suggestive of previous bullae or pustules. The canker sore belongs in the group of lesions of this type. Herpangina, called "aphthous pharyngitis" by Breese, and "vesicular pharyngitis" by Hoerr and associates, belongs to the group of diseases characterized by vesicular lesions and, as was suggested in my articles, is a specific disease.

John Zahorsky, M.D., St. Louis.

News and Comment

GENERAL NEWS

National Association for Nursery Education.—The National Association for Nursery Education will meet at the Book-Cadillac Hotel, Detroit, from Oct. 24 to 27, 1941.

DEATHS

Dr. Thomas D. Jones, of Richmond, Va., assistant professor of pediatrics at the Medical College of Virginia, died of acute lymphatic leukemia, on June 12.

Obituaries

THOMAS S. SOUTHWORTH, M.D.

1861-1940

Dr. Thomas S. Southworth was born in Springfield, Mass., in 1861. He prepared for college at Phillips Academy, Andover, Mass., and entered Yale University, from which he was graduated in the class of 1883.

After traveling and studying chemistry at the University of Göttingen, he enrolled in the medical department of Columbia College, New York, later called Columbia University College of Physicians and Surgeons, from which he received the degree of Doctor of Medicine in 1887. He ranked among the first ten students in the final examination. He won first place in a competitive examination for the St. Luke's Hospital service and served as medical intern in 1887 and 1888. He was appointed for a one year's service as surgical intern at Chambers' Street Hospital in 1888.

After a year spent in study in the hospitals of Vienna and the Rotunda Hospital of Dublin, he began the practice of medicine in New York city. Shortly afterward he began pediatric work with Dr. L. Emmett Holt, for the first edition of whose textbook on diseases of children he compiled the index and contributed material for the chapter on diseases of the blood; he was among the first to use Ehrlich's stains for blood cells, with which he had become acquainted in Vienna.

He was at various times connected with the Vanderbilt Clinics and the New York Polyclinic Medical School and Hospital. He was attending pediatrician at the Misericordia Hospital and pathologist, attending physician and, finally, consulting physician at the New York Nursery and Childs Hospital.

Dr. Southworth held the position of chairman of the Section on Diseases of Children of the American Medical Association, 1909; chairman of the pediatric section of the Medical Society of the State of New York, 1914; president of the Medical Association of the Greater City of New York, 1914-1917; president of the American Pediatric Society, 1920, and president of the Hospital Graduates, 1912. He was a member of the American Medical Association, the New York Academy of Medicine and the New York state and county medical societies.

Dr. Southworth's contributions to pediatric literature covered a wide range of subjects, largely relating to young infants. He was not a collaborator. He was a keen observer and an admirable clinician, and his contributions bore evidences of a masterly mind for clinical research.

Dr. Southworth married Jean Ponton Hamilton in 1903. She died Dec. 2, 1924. There is one son, Dr. Hamilton Southworth, of New York city.

Physicians practicing the same specialty in the same community are often placed in positions in which professional relations become a bit strained. Dr. Southworth as a competitor in private practice and as an associate in hospital work will always be remembered by his colleagues as outstanding in his consideration for others, in his ability as a physician and in his high character as a citizen.

C. G. K.

ALBERT GRAEME MITCHELL, M.D.

1889–1941

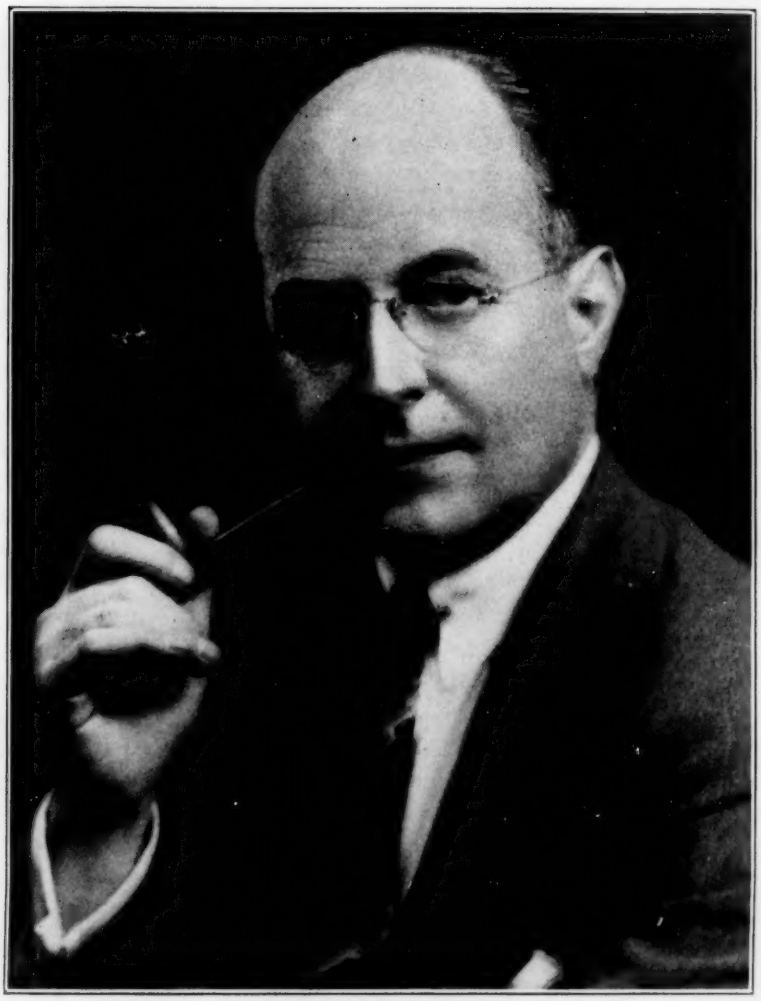
Albert Graeme Mitchell was born in Salem, Mass., Feb. 22, 1889, the son of Frederick Albert and Marie Graham Mitchell. He had his early education in the Central High School of Philadelphia and graduated from the University of Pennsylvania School of Medicine in 1910.

He was resident physician at Presbyterian Hospital, Philadelphia, for eighteen months in 1910 and 1911 and chief resident for eleven months in 1911 and 1912. The next year he served as resident physician at Babies' Hospital and then spent three months at the Harvard Medical School, studying under Dr. John Lovett Morse, Dr. Fritz Talbot and Dr. Otto Folin.

During the World War he was a captain of the Medical Corps of the United States Army, adjutant of hospital unit A and superintendent and medical director of the American Hospital for Civilians, Neufchâteau, France. He served with the One Hundred and Forty-Ninth Machine Gun Battalion of the Forty-Second Division in the San Mihiel and Argonne offensives and with the Army of Occupation. He was later made a major in the Medical Reserve Corps, which commission he resigned in 1929.

In 1919 Dr. Mitchell became instructor in pediatrics at the University of Pennsylvania School of Medicine. In 1924 he accepted the B. K. Rachford Professorship in Pediatrics at the University of Cincinnati College of Medicine, which he held until the time of his death. During this time, he was director of pediatrics and of contagious diseases at the Cincinnati General Hospital and medical director and chief of staff of the Children's Hospital, Cincinnati. Since 1928 he had been director of the Children's Hospital Research Foundation, medical director of the Babies' Milk Fund Association of Cincinnati and consulting pediatrician to the Ohio Soldiers' and Sailors' Orphans' Home Hospital, at Xenia, Ohio. Among the various medical societies to which Dr. Mitchell belonged were the American Pediatric Society, the Society for Pediatric Research and the American Academy of Pediatrics. He was a member of the executive board of the last-named organization and an honorary member of the St. Louis Pediatric Society and of "Galen's" Honorary Medical Society, Ann Arbor, Mich. Alpha Mu Pi Omega, was his medical fraternity and he belonged to Sigma Xi and Alpha Omega Alpha, honorary societies.

Dr. Mitchell was a prolific writer, having contributed approximately one hundred and fifty articles to medical literature, but he will be best known probably for the textbook, "Diseases of Infants and Children," which he wrote in collaboration with John Price Crozer Griffith. For



ALBERT GRAEME MITCHELL, M.D.
1889–1941

many years he had been a member of the Editorial Board of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

His avocation was art. He was early interested in water color painting, but later confined his work to etching and dry point, in which he attained an enviable degree of proficiency.

On Oct. 2, 1920, he was married to Adele Florence Wentz. His wife and their two children, Marie Graham and Kathryn Wentz Mitchell, together with his father, survive him.

Dr. Mitchell was a rare character. He had so many good qualities that it is difficult to designate any as outstanding, but in looking over his career, one cannot but be impressed with his capacity for work and accomplishment.

On the platform, whether delivering an address, reading a paper or conducting discussion, he was probably the most popular pediatrician of today. He not only had something to say, but knew how to say it. His fine sense of humor and kindly wit, added to his knowledge and intellectual attainments, made him peculiarly adapted for the presentation of any subject in which he took interest. He was self assured, but not egotistic. Whether in a crowd or in private conversation, he was always kindly, always lively and always contributing. His great executive ability was reflected in the development of his departments at the University of Cincinnati and the Children's Hospital. He had the happy faculty of interesting people in high places without losing his independence in any way. That he enjoyed the lighter side of life is witnessed by his collection of medical caricatures and his rare ability as a raconteur.

All these attributes he showed the world, but the devotion which he inspired in his family and at Children's Hospital in his board of managers, in the medical men by whom he was surrounded and in the younger men who sat at his feet, can only be estimated by the sorrow which has followed his going in the place that he loved the best. One young pediatrician has said that Dr. Mitchell represented the link between the clinical man of yesterday and the laboratory investigator of today. This is probably true. No man attained more in American pediatrics than did A. Graeme Mitchell, and no man's loss will be as universally felt as his.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

THE DISTRIBUTION OF GLUCOSE [DEXTROSE] BETWEEN CELLS AND SERUM: FURTHER EXPERIMENTS WITH HIGH CONCENTRATIONS OF GLUCOSE. KALMEN A. KLINGHOFFER, Am. J. Physiol. **130**:89 (July) 1940.

When concentrated solutions of dextrose are added to blood there is a marked discrepancy between the amount of dextrose taken up by the cells and that remaining in the serum. The disproportion tends to diminish with time but does not disappear completely. The limiting factors in the penetrability of the cell membrane to dextrose are discussed but are not precisely defined. It is demonstrated, however, that despite the discrepancy in the distribution of dextrose, osmolar equality between the cells and the serum is still maintained.

NOURSE, Cleveland.

THE INFLUENCE OF ADRENALECTOMY AND OF FASTING ON THE INTESTINAL ABSORPTION OF CARBOHYDRATES. ROSE MARRAZZI, Am. J. Physiol. **131**:36 (Nov.) 1940.

The author reaches the conclusion that the reduction of food intake, induced by postoperative anorexia, and the surgical manipulation can account for the decrease in the absorption of dextrose in adrenalectomized animals. It is probable, in fact, that anorexia alone can account for it.

NOURSE, Cleveland.

THE FEEDING OF CHILDREN. J. C. SPENCE, Brit. M. J. **2**:93 (July 20) 1940.

An outline of the actual food requirements of children is given, with special reference to the necessity for accurate measurements in accordance with age, the quantity needed and the caloric requirements.

ROYSTER, University, Va.

OBSERVATION OF SUCKING HABITS OF NEWBORN BABIES AND INFANTS. ELSBETH V. SCHNIZER, Deutsche Zahn- Mund- und Kieferheilkunde **6**:412, (July) 1939.

The initial stages of finger or fist sucking in 116 babies 1 to 12 days old and in 53 infants up to 9 months of age are systematically checked as to frequency, intensity and special kind of sucking habits. General health and attitude are also taken into consideration. Sick and prematurely born babies do not suck at all. Occasional mild sucking in early days develops gradually into an individual type of habit.

Department of Orthodontia, University of Illinois. [ANGLE ORTHODONTIST]

FEEDING CHILDREN IN WARTIME. FRANZ HAMBURGER, Wien. klin. Wchnschr. **28**:559 (July 12) 1940.

Hamburger shows that war presents special problems in the feeding of children, not only with regard to nutritive value of food but with regard to its vitamin content. The German retrieving system provides sufficient milk and butter to give children the necessary vitamin A; vitamins B_1 and B_2 are obtained from cornbread made from wheat bread and also from rye and whole wheat. Ascorbic acid in doses as small as 15 to 20 mg. daily is believed by the author to give enough vitamin C; other sources in winter, if citrus fruits are not available, are apples, kraut, turnips and especially carrots. In winter, when the lack of sunshine makes artificial vitamin D therapy necessary, some vitamin D preparation can be given; it is important to give sufficiently large doses.

In times when people are restricted in their diet, the psychologic factor of eating often is recommended by the author. He thinks that 40 per cent of the diet should be eaten at noon and 30 per cent in the evening. The other 30 per cent he would divide as follows: breakfast, 15 per cent; second breakfast, 5 per cent; afternoon tea, 10 per cent.

Sick children instinctively eat less and usually have a desire for fruit juices; in the latter respect war may present a problem. If, in addition, the child has an appetite for milk and meat, it may be difficult to satisfy him; however, 0.5 to 1 liter of milk daily, 125 Gm. of butter and 500 Gm. of meat per week are sufficient for the needs of any sick child, even if anemia is present. ABT, Chicago.

METABOLIC STUDIES ON THE ROASTED SOYBEAN MEAL AS AN INFANT FOOD. C. FAN, THERESA T. WOO and F. T. CHU, Chinese M. J. **58**:53 (July) 1940.

Two infants were fed certain soy bean mixtures, and metabolism studies were made. Determinations were made of the balances for nitrogen, calcium and phosphorus and also of the levels of serum calcium, inorganic phosphorus and phosphatase. The reader is referred to the original article for the results.

NEFF, Kansas City, Mo.

THE STATE OF NUTRITION OF SO-CALLED UNDERWEIGHT SCHOOL CHILDREN. A. RUOTSALAINEN, Acta pædiat. **27**:437, 1940.

Referring to his own previous contributions, which have appeared in the *Acta Pædiatrica* and elsewhere, Routsalainen again calls attention to the widespread misunderstanding which has arisen as a consequence of the general use of the weight/height quotient as a measure of the nutritional status of children. The ratio is not a dependable index of the thickness of the panniculus adiposus; this has been demonstrated by numerous observations on the thickness of the subcutaneous fat of the abdomen and the back of children judged to be undernourished by the weight/height standard. For example, of 457 Finnish school children classified as underweight, the author found that 13 per cent had more than the average thickness of subcutaneous fat and 47 per cent the average thickness; only 40 per cent were thin in this respect as well as underweight. Additional measurements on a group of 6,005 school children, which are reported in detail, have confirmed the earlier results and have added the information that the correlation between thinness and underweight varies considerably from school to school. In one district, for example, only 9 per cent of the underweight children exhibited less than average thickness of the subcutaneous fat. The reasons for the discrepancy are discussed, and it is recommended that the practice of segregating certain children for special care on the basis of a low weight/height ratio be abandoned. As a substitute, a more comprehensive policy of general nutritional supervision is recommended.

MCCUNE, New York.

Vitamins; Avitaminoses

DARK ADAPTATION AND EXPERIMENTAL HUMAN VITAMIN A DEFICIENCY. SELIG HECHT and JOSEPH MANDELBAUM, Am. J. Physiol. **130**:651 (Oct.) 1940.

Measurements of the dark adaptation of 17 young men made before, during and after a period of ingesting a diet deficient in vitamin A showed that the visual function of both the cones and the rods of the retina were affected by the diet. Of the 17 subjects, 14 responded to consumption of the deficient diet with an immediate and unmistakable rise in the visual threshold, which continued for as long as they remained on the diet. None of the subjects had cutaneous symptoms, and only the 2 most severely affected recorded a subjective awareness of their raised visual thresholds. Partial restoration of the visual threshold was accomplished in some subjects by administration of a single large dose of vitamin A. Permanent recovery from the effects of the diet deficient in vitamin A was slow; it required from six weeks to more than three months.

NOURSE, Cleveland.

CEREBROSPINAL FLUID PRESSURE AND VITAMIN A DEFICIENCY. L. A. MOORE and J. F. SYKES, Am. J. Physiol. **130**:684 (Oct.) 1940.

A deficiency of vitamin A in the ration of the young bovine produces an increase in the pressure of the cerebrospinal fluid which is accompanied by papilledema, nyctalopia, syncope and incoordination. On return to a normal diet, the cerebrospinal pressure slowly returns to normal and the other disturbances disappear.

NOURSE, Cleveland.

VITAMIN C STUDIES: I. THE EFFECT OF VITAMIN P (CITRIN) ON VITAMIN C–DEFICIENT GUINEA PIGS. L. E. DETRICK, M. S. DUNN, W. L. MCNAMARA and M. E. HUBBARD, J. Lab. & Clin. Med. **25**:684 (April) 1940.

The authors studied the effect of vitamin P (citrin) on vitamin C–deficient guinea pigs. Their experiment showed that citrin, isolated by the technic of Armentano, did not decrease the hemorrhagic lesion of the syndrome of scurvy or prolong the life of the scorbutic guinea pigs. READING, Galveston, Texas.

NICOTINIC ACID POTENCY OF FOOD MATERIALS AND CERTAIN CHEMICAL COMPOUNDS. HARRY A. WAISMAN, OLAF MICKELSEN, J. M. MCKIBBIN and C. A. ELVEHJEM, J. Nutrition **19**:483 (May) 1940.

These Wisconsin investigators made a biologic assay of the nicotinic acid content of various food materials by the use of dogs with blacktongue maintained on the modified Goldberger diet. Meats and meat products showed a nicotinic acid content ranging from 10 to 110 mg. per hundred grams of dry tissue. Liver extract contained 200 to 450 mg. of nicotinic acid per hundred grams and yeast 30 to 100 mg. As a substitute for nicotinic acid when injected, quinolinic acid was found to be inactive. FREDEEN, Kansas City, Mo.

TREATMENT OF RICKETS WITH MINIMAL VIOSTEROL DOSAGE. ALANZO DEG. SMITH and NOLAN A. OWENS, J. Pediat. **16**:76 (Jan.) 1940.

Thirteen Negro infants 8 to 28 months of age, with moderate and severe rickets, were hospitalized under controlled conditions for fifty-six days. During a two week observation period there was absence of spontaneous healing of rickets. After this period of observation each child was given daily 800 U. S. P. units of vitamin D in the form of viosterol in oil. All infants but 4 with severe rickets showed beginning healing at the end of the first week of therapy. Eight of the 13 were almost completely healed at the end of the sixth week.

RAUH, Cincinnati.

THE BLACKTONGUE CURATIVE EFFECT OF PYRIDINE-B-CARBOXYLIC ACID DIETHYLAMIDE (CORAMINE). DAVID T. SMITH, GEORGE MARGOLIS and LESTER H. MARGOLIS, J. Pharmacol. & Exper. Therap. **68**:458 (April) 1940.

Nicotinic acid has proved to be very effective for blacktongue in dogs and for the similar condition in human pellagrins. Because of their close chemical relation coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) was tried in dogs with blacktongue and proved very effective.

PILCHER, Cleveland.

NEGATIVE EFFECT OF SYNTHETIC VITAMIN B_6 HYDROCHLORIDE IN NUTRITIONAL DEFICIENCY IN MAN. R. KARK, E. L. LOZNER and A. P. MEIKLEJOHN, Proc. Soc. Exper. Biol. & Med. **43**:97 (Jan.) 1940.

Six patients, 2 with endemic pellagra, 2 with "alcoholic" pellagra, 1 with "idiopathic" hypochromic anemia and 1 with nutritional macrocytic anemia, were

given synthetic vitamin B_6 hydrochloride. In none of the patients was any improvement noted in the anemia or in the signs or the symptoms of these patients. No toxic symptoms occurred in spite of 350 to 940 mg. doses by mouth and 130 to 1,140 mg., intravenously, for from six to twenty-two days. Spies and co-workers (Spies, T. D.; Bean, W. B., and Ashe, W. F.: Note on Use of Vitamin B_6 in Human Nutrition, *J. A. M. A.* **112**:2414 [June 10] 1939) previously had reported favorable results with 50 mg. doses of vitamin B_6 in 4 patients with pellagra who when maintained on a deficient diet plus nicotinic acid, riboflavin and thiamine chloride continued to have symptoms of nervousness, insomnia, abdominal pain, weakness and difficulty in walking.

HANSEN, Minneapolis.

VITAMINS D_2 AND D_3 IN INFANTILE RICKETS. NOAH MORRIS and MARY M. STEVENSON, Lancet **2**:876 (Oct. 21) 1939.

Bills pointed out that the properties of vitamin D are exhibited by ten different derivatives of sterol. From the practical point of view only two need be considered at present—vitamins D_2 and D_3. Vitamin D_2, better known in England as calciferol, is formed by the irradiation of ergosterol, a substance which is essentially a constituent of the sterols of plants, although its presence has also been demonstrated in eggs. Vitamin D_3, on the other hand, has as its provitamin 7-dehydrocholesterol, which has been isolated from animal sterols and is present in relatively high concentration in tunny liver and halibut liver oils.

In the present study an attempt was made to compare the potency of crystalline vitamins D_2 and D_3. It was felt that any differences in the effects of the two vitamins would be best detected if the dosage were low; accordingly 2,000 U. S. P. units a day were given to each patient, irrespective of age and weight.

The course of healing in 12 infants and children with active rickets was studied by serial roentgen study of the wrists and by estimation of the level of plasma phosphatase. No significant difference was found between the therapeutic effects of these two vitamins.

LANGMANN, New York.

BERIBERI IN CHILDREN UNDER ONE YEAR OF AGE IN CUBA. ARTURO J. ABALÍ and ESCOBAR ACÉS, Arch. de med. inf. **9**:215 (Oct.-Dec.) 1940.

Beriberi was not recognized until recently in Cuba, and it is probably much more common than was once thought. It is seen usually during the third and fourth month of life in breast-fed infants and is often initiated by an infection of the respiratory tract. Some infants with the disease have not responded to vitamin B_1 therapy; so other vitamin factors may be involved. Those cases in which there are cardiac complications carry the most serious prognosis. There are symptomatic differences between the form of the disease observed in Cuba and that seen in Japan and the Philippine Islands, which no doubt are due to differences in basic food constituents.

SANFORD, Chicago.

PARENTERAL EFFECTIVENESS OF VITAMIN D_2 AND VITAMIN D_3 FOR RICKETS. A. NITSCHKE, Ztschr. f. Kinderh. **61**:385 (Oct. 5) 1939.

In agreement with the findings of three other authors, Nitschke's results with parenteral, intracutaneous and percutaneous administration of vitamin D_2 as found in vigantol (a preparation of irradiated ergosterol) were almost entirely negative. Results with vitamin D_3 as found in cod liver oil were good. Favorable results with parenteral administration of vitamin D_2 can probably be explained on the basis of admixture of vitamin D_3. The effectiveness of vitamin D_2 administered parenterally is probably due to its metabolic transformation to vitamin D_3.

SIEMSEN, Chicago.

VITAMIN CONTENT IN "BORS." D. TIMUS and MARIA GEORGESCU, Med. inf., Bucharest **1**:361 (Sept.-Oct.) 1939.

The authors sought to determine the vitamin content of "bors," an aqueous food resulting from the fermentation of wheat at a temperature of 37 to 40 C. for twenty-four to forty-eight hours. The real value of the product rests in the vitamins of group B, especially vitamin B_1, since the nutritive values are minimum. By feeding "bors" to scorbutic rabbits the authors failed to demonstrate the presence of vitamin C. By feeding it to pigeons with beriberi they were able to show that 5 cm. of "bors" contains 1 international unit of vitamin B_1. They also established the presence of vitamin G (B_2). They concluded that the therapeutic effect of "bors" in cases of anorexia of convalescence and gastrointestinal atony is explained as well by eupeptic action due to the acids of fermentation as by the presence of vitamin B_1 and especially of vitamin G (B_2).

FROM AUTHORS' SUMMARY.

THE ROLE OF VITAMIN D IN THE CALCIUM METABOLISM IN OSTEOMALACIA. S. H. LIU, Chinese M. J. **57**:101 (Feb.) 1940.

Many inhabitants in the neighborhood of Peiping live chiefly on cereal, soy beans and vegetables. This diet produces definite evidence of vitamin D disturbance if the person has not had sufficient protective exposure to the sun's rays. Calcium metabolic studies show that there is benefit when foods containing vitamin D, such as eggs and milk, are added.

The writer dwells principally on the added vitamin requirements during pregnancy and lactation. It is shown that the infant's metabolism reflects that of the mother during variations in the vitamin D content of the breast milk. In 1 case reported a mother had suffered for years with general osteoporosis. During pregnancy her mineral retention was improved by the use of a vitamin D (irradiated ergosterol) preparation (vigantol). Seventeen days after delivery she again showed a negative balance for calcium, which lasted for two or three months, until vitamin D was again administered. At birth the infant showed no rarefaction in the bones, probably owing to protection by vitamin D received by the mother during the latter part of pregnancy. Afterward the mother's calcium became disturbed again and the nursing infant was found to have a slight decrease in calcium retention. There occurred a progressive decrease in the child's concentration of urinary calcium, going on to almost complete disappearance, but there was a steady rise in the calcium content of the stool. The author concludes that there must be provision of vitamin D, calcium and sunlight during pregnancy and lactation if the fetus and the child are to be protected from rickets.

NEFF, Kansas City, Mo.

THE FRUIT OF THE WILD ROSE AS A SOURCE OF VITAMIN C. B. HAMMER and J. SCHRÖDERHEIM, Acta Pædiat. **25**:102, 1939.

In their quest for a native natural source of vitamin C the northern nations have investigated many foods. Previous examinations have indicated that the fruit of the wild rose, the hip, fulfils the following criteria: widespread availability, generous vitamin C content (which is not significantly lowered during storage), ease of preservation, transportation and preparation for consumption and, finally, palatableness and cheapness. Preparations of this fruit have been used successfully in the Norrtull-Krankenhaus, Stockholm, and to an increasing degree by the public for some time. The present investigation was stimulated by certain difficulties that have been encountered. The determinations of vitamin C were made by the dichlorphenolindophenol method in the presence of metaphosphoric acid. It was found that if the berries were obtained at the right season from plants of suitable strain, prepared properly and served without undue delay after being made into tea or broth, the wild rose fruit constitutes an

admirable source of vitamin C. Failure to observe the precautions described renders it unsatisfactory. The reader is referred to the original articles for essential details too numerous to be abstracted.

McCUNE, New York.

Hygiene; Growth and Nutrition; Public Health

BIRTH REGISTRATION IN SOUTH CAROLINA. HALBERT L. DUNN, J. South Carolina M. A. **36**:14 (Jan.) 1940.

As a reviewer of this article and a South Carolinian I am greatly embarrassed. There were eleven counties out of the total 46 of the state investigated, showing that only 75.4 per cent of the births of children under 1 year of age had been registered. These counties constituted an excellent cross section of the state, as every part of the state was included. There is no better way to prove that one is oneself than by the birth registration. I believe there will be a marked improvement in this respect within the next three years.

WESTON, Columbia, S. C.

Prematurity and Congenital Deformities

CONGENITAL CRANIOFACIAL MALFORMATION (PTEROSCHISIS, ENCEPHALOCELE AND HYPERTELORISM). O. ARMENIO, Arch. ital. di otol. **52**:251 (May) 1940.

Armenio reports a case of congenital deformity in a boy aged 3 years represented by dehiscence of the right lateral wall of the nose, flattening and broadening of the root of the nose and bilateral frontal encephalocele. The two inner canthi were 55 mm. apart. The Wassermann reaction was negative. The nasal bones could be palpated, and the interior of the nose was normal. The malformations are said to be due to a fault of development of the precordial cartilage, dependent on a hypophysial, endocrine dysfunction initiated during intrauterine life.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

USE OF CORAMINE IN THE CIRCULATORY AND RESPIRATORY DISTURBANCES OF PREMATURE INFANTS. G. ROI, Med. ital. **21**:75 (Feb.) 1940.

The author reviews the action of coramine. He administered coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) to 32 premature infants, 9 of whom weighed less than 1,800 Gm. He gave 10 to 20 drops three to four times per day by mouth. Administration was continued until the author thought that there was no further need. During the treatment the attacks of asphyxia were less frequent and less intense. The respirations became more regular and the heart sounds louder. The babies became more lively and better able to nurse. The gain in weight was more regular and rapid. The mortality in this group of premature infants was 12 per cent.

MARTOCCIO, Utica, N. Y.

Newborn

ERYTHROBLASTIC ANEMIA OF THE NEWBORN. BEN SHAPIRO and MICHAEL BEVILACQUA, Arch. Pediat. **57**:659 (Oct.) 1940.

Seven cases are reported. Six patients made good recoveries after receiving transfusions and 1 died.

ORR, Buffalo.

ABSENCE OF GROSS ADRENAL TISSUE IN THE NEWBORN: REPORT OF A CASE. GARDNER N. COBB, Arch. Pediat. **57**:739 (Nov.) 1940.

Autopsy on a boy aged 22 days showed no evidence of adrenal tissue.

ORR, Buffalo.

STREPTOCOCCUS VIRIDANS SEPSIS NEONATORUM WITH MENINGITIS; RECOVERY FOLLOWING SULFAPYRIDINE. JOSEPH GREENGARD, WILLIAM B. RAYCRAFT and WILLIAM G. MOTELL, Arch. Pediat. **57**:770 (Dec.) 1940.

A case of Streptococcus viridans sepsis of the newborn with meningitis is reported. The infant made a complete recovery after the administration of 36.4 Gm. of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) over a period of one month.

ORR, Buffalo.

DEATH IN NEWBORN AND STILLBORN INFANTS. JAMES S. P. BECK, New England J. Med. **220**:558 (March 30) 1939.

In a small series of 25 dead infants, varying in gestational age from 5 to 9 months, for whom there were available autopsy and clinical data, the cause of death of 64 per cent was traceable to intrauterine disturbances other than those related to the fetus or to difficult delivery. The remaining 36 per cent consisted of congenital malformations incompatible with extrauterine life (12 per cent), injuries due to difficult labor (20 per cent) and syphilis (4 per cent).

The various conditions with their probable causes are discussed in detail.

GENGENBACH, Denver.

ANEMIAS OF PREMATURE AND NEWBORN INFANTS. LUIS CID R., Arch. d. Hosp. niños Roberto del Rio **9**:174 (Oct.) 1940.

The anemias are classified into two groups: symptomatic anemias, which include the posthemorrhagic, septic and syphilitic types, and the constitutional anemias, which include the hypochromic, erythroblastic and hereditary types.

SANFORD, Chicago.

MORBUS HAEMORRHAGICUS NEONATORUM (HYPOPROTHROMBINEMIA NEONATORUM). L. SALOMONSEN, Acta pædiat. (supp. 1) **27**:1, 1939.

On the foundation of a personal experience of 66 carefully observed cases supplemented by a thoroughgoing review of the literature, Salomonsen has constructed a highly informative monograph on hemorrhagic disease of the newborn. Although much of the substance is available in the better textbooks, it is seldom procurable in such convincingly documented form.

Hemorrhagic disease of the newborn is encountered in about 0.7 per cent of newborn infants; it occurs with equal frequency in the two sexes and is somewhat more common in winter than in summer. The onset is usually on the second or third day of life but may take place as late as the second week; with occasional exceptions the duration does not exceed three days. As in hemophilia, trauma is peculiarly important in precipitating bleeding. The most frequent sites of hemorrhage are the skin, the umbilicus, the gastrointestinal mucosa, the brain and the mucous membranes of the mouth and nose. The disease is responsible for delayed intracranial hemorrhage in a considerable number of cases. The sites of bleeding are characteristically multiple. Corresponding to lack of alteration of capillary permeability, petechiae do not occur. Although anemia may develop, there is no alteration of the white blood cell count or of the blood platelets. The essential diagnostic features are prolongation of the clotting time and increase of the prothrombin time. As both of these measurements exhibit transitory increase during the first week of life even in healthy infants, the range of values obtained in hemorrhagic disease does not show clearcut demarcation from those that may be regarded as physiologic. As a consequence, transitional cases are encountered, representing the borderline between hemorrhagic disease and health. Transfusion is specific and produces rapid cessation of bleeding, with restoration of the indexes of coagulation to normal values. Intramuscular injection of blood is much less

efficient. The benefit of transfusion is often temporary. The unpublished experience of Nygaard with 7 cases has shown that dramatic cure can be accomplished by the use of vitamin K. Although the recent experience with vitamin K suggests that the disease is due to exogenous vitamin deficiency, it remains possible that its occurrence may depend on inability to produce the vitamin in the alimentary tract through bacterial action or to absorb it from the intestines into the body. Defective function of the liver may participate in its pathogenesis. The summaries of 66 cases and a lengthy bibliography are appended. McCune, New York.

Acute Contagious Diseases

Human Scarlatinal Streptococci in Monkeys. Paul L. Boisvert, J. Bact. **39**:727 (June) 1940.

It is a known fact that hemolytic streptococci can be isolated from animals with spontaneous infections. In addition, the organism has been found in some animals as a part of the normal flora. In most instances the animal strains have been easily distinguished from those of human origin. In this report of the author 3 rhesus monkeys which had spontaneous infections (2 facial erysipelas, 1 an axillary abscess) and a fourth animal which was accidentally infected by the intraperiteoneal administration of the drug were closely observed and studied from the bacteriologic viewpoint. A hemolytic streptococcus was obtained in all 4 cases. The cultures yielded a pure growth of the organism. In each instance the monkey was found to be infected by a streptococcus which could not be differentiated from that of scarlet fever. In other words, the author feels that he has evidence that these monkeys were infected by strains of the hemolytic streptococci indistinguishable from those found in scarlet fever and other severe human streptococcic diseases. This observation may have an important bearing on future studies concerning the spread of disease from man to animal and from animal to man.

Stoesser, Minneapolis.

Prophylaxis and Treatment of Poliomyelitis with Neoprontosil. W. M. Rhett, J. Pediat. **16**:326 (March) 1940.

During an epidemic of poliomyelitis 440 acutely ill children were given azosulfamide (neoprontosil; disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate) in the dosage of 1 grain (0.064 Gm.) per pound of body weight per day. Only 1 of these children showed development of paralysis. The paralysis developed on the fifth day of illness and was transient. The full dosage of the drug had not been maintained, and when it was resumed, the symptoms subsided, and by the end of three weeks the paralytic involvement had completely cleared. In 2 other children in whom the full dosage of azosulfamide had not been maintained, meningeal symptoms developed on the fifth day of illness; these symptoms subsided without paralysis on resumption of the full dosage of the drug. Fourteen cases of poliomyelitis are reported in which azosulfamide was given in the preparalytic stage. In only 1 case did paralysis develop, and it was transient. In 8 cases in which a clinical diagnosis of meningeal involvement was made, this subsided with azosulfamide medication, without paralysis. Eleven patients with paralysis were treated with azosulfamide. Toxic symptoms subsided within twenty-four to forty-eight hours, and no advance in paralytic involvement developed after an adequate dosage of the drug had been maintained for twenty-four to forty-eight hours. In 2 of these children the poliomyelitis was of the fulminating type, with involvement of the respiratory musculature, necessitating use of the respirator. One of these children died two months later, during an attack of asthma.

Rauh, Cincinnati. [From Author's Summary]

EFFECT OF CHLORINATION OF CITY WATER ON VIRUS OF POLIOMYELITIS. J. E. KEMPF and M. H. SOULE, Proc. Soc. Exper. Biol. & Med. **44**:431 (June) 1940.

A 10 per cent emulsion of spinal cord from monkeys affected with poliomyelitis was prepared and centrifuged. The supernatant suspension was added to fresh water containing various concentrations of chlorine and allowed to act for various lengths of time; then it was injected intracranially into monkeys. These studies disclosed that chlorine in a concentration of 0.5 part per million, which is in excess of the amount usually employed in municipal practice, did not inactivate the virus of poliomyelitis in one and one-half hours. HANSEN, Minneapolis.

SUMMARY OF CURRENT PREVALENCE OF COMMUNICABLE DISEASES. Pub. Health Rep. **55**:1193 (July 5) 1940.

For the period ending June 15, 1940, influenza showed an increase of 20 per cent above the median, and poliomyelitis was also slightly above the median. Of the 179 cases reported, Washington reported 77 and California 44. All other diseases were below the median. The average mortality from all causes was 10.9 per thousand, the average being 11. SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **55**:1555 (Aug. 30) 1940.

For the period of July 14 to Aug. 10, 1940, influenza and measles showed an increase above the median incidence. This was found in the Atlantic regions. All other diseases were below the median. The mortality from all causes was 10.8 per thousand. This is 0.5 above the average. SANFORD, Chicago.

PROPHYLACTIC IOCULATION AGAINST WHOOPING COUGH. I. H. MACLEAN, Proc. Roy. Soc. Med. **33**:425 (May) 1940.

The following is the author's summary of this paper:

"The best age to start immunization is during the first or second year of the child's life.

"Among the inoculated children the attack rate is less than 5 per cent and the communicability rate is less than 10 per cent as against 60 to 90 per cent in the control groups.

"The primary immunizing dose of vaccine need only be sufficient to establish a sound basal immunity. Once . . . established the immunity can easily be stimulated by subsequent doses of vaccine, which act in the nature of a 'secondary response.'

"By using this 'secondary response' and a total dosage of only 16,000 million organisms, apparently good immunity was attained. In a test group of 513 children with 46 known exposures and 45 suspected exposures not a single case of whooping cough occurred. In a control group of 154 exposures 89 cases of the disease occurred.

"An additional dose of 4,000 million organisms should be given subsequent to the immunization course when the child is known to have been exposed to the infection, or starts school life.

"If the disease occurs in a vaccinated child, it is usually mild or atypical.

"The only reliable vaccine is one made from a suspension of killed Phase I strains of H. pertussis." WILLIAMSON, New Orleans.

THE LEUKOCYTIC FORMULA IN ACUTE POLIOMYELITIS. RAYMOND MEYER, Rev. franç. de pédiat. **14**:135, 1938.

The author has studied the leukocytic formula in 57 cases of poliomyelitis and also in a varying number of cases of other conditions which might be con-

fused with it. He has come to the following conclusions: In cases of poliomyelitis, during the period of invasion and the first day of paralysis there is slight leukocytosis, with a slight increase in polymorphonuclear cells. This gives way little by little to slight lymphocytosis, with the occasional appearance of rare plasmocytes and a monocyte count of 9 per cent or more. The eosinophils and basophils tend to disappear. After the establishment of the paralysis, the leukocytic formula returns to normal, or there may be slight leukopenia. The only other condition the author found which might be confusing from the standpoint of the blood picture was acrodynia, but the gradual onset makes the clinical differentiation easy.

LESLIE, Evanston, Ill.

THE NITROGEN CONTENT OF THE BLOOD IN THE PROGNOSIS OF MALIGNANT DIPHTHERIA. A. SEVERINO, Med. ital. **20**:429 (Sept.) 1939.

The blood of 400 patients with diphtheria was examined for the urea content by the method of Kowarsky. The patients were aged from 2 to 14 years. The author concludes that determination of the nitrogen content of the blood is of great importance in determining the prognosis of malignant diphtheria. A value for urea of 1.0 to 1.5 Gm. per thousand grams carried a mortality of 80 per cent. A value of 1.5 to 2.5 Gm. per thousand grams carried a mortality of 100 per cent.

MARTOCCIO, Utica, N. Y.

DIAGNOSTIC VALUE OF FINDING THE BORDET GENGOU BACILLUS (HAEMOPHILUS PERTUSSIS) IN CHILDREN WITH SEVERE COUGH. F. MORGANTI, Riv. di clin. pediat. **38**:284 (May) 1940.

Dechigi pigeon's blood agar will differentiate between Haemophilus influenzae and Haemophilus pertussis; the former shows a rapid growth of flat, dewlike transparent colonies, while the latter shows small, slowly growing, spherical, nontransparent hemolytic colonies.

Cough plates on this medium have proved helpful in the diagnosis of pertussis.

HIGGINS, Boston.

PROPHYLAXIS OF SCARLET FEVER. WERNER SCHULTZ, Deutsche med. Wchnschr. **66**:396 (April 12) 1940.

The author suggests passive immunization with human serum in preference to horse serum. Lichtenstein proved that whereas convalescent human serum gave 80 per cent of positive bleaching reactions, serum of old persons, irrespective of whether they had or had not had scarlet fever, gave a positive test reaction in 88 per cent of the cases. Therefore, it is unnecessary to use convalescent serum for passive immunization. Normal serum of elderly adults is just as effective and much more readily available.

For active immunization the author suggests scarlet fever toxoid which is made of 500,000,000 scarlet fever streptococci and contains 1,000 skin test doses per cubic centimeter. Local reactions are to be expected from this test.

As the aforementioned two methods are simple and effective, the eradication of scarlet fever is a matter of organization.

KEREZTURI, New York.

FEVER THERAPY (PYRIFER, MALARIA) IN POLIOMYELITIS. H. KOHL, Kinderärztl. Praxis **11**:278 (Sept.) 1940.

Kohl used malaria therapy as well as pyrifer to produce fever. Pyrifer is a protein preparation obtained from bacilli similar to Bacillus coli and is manufactured by Aristopharm, Basel, Switzerland. In contradiction to the results obtained by other authors, Kohl did not observe any convincing effects from artificial fever therapy in cases of poliomyelitis.

HEYMANN, Cleveland.

TREATMENT OF EPIDEMIC MENINGITIS. D. KOCH, München. med. Wchnschr. **87**:704 (June 28) 1940.

Sulfanilamide therapy greatly improved the results of treatment of meningococcic meningitis. Koch obtained better results with sulfapyridine. In cases of mild involvement sulfapyridine and lumbar puncture alone are sufficient. In cases of severe involvement the best results are obtained by combining specific serotherapy and sulfapyridine.

BRAHDY, Mount Vernon, N. Y.

INFLUENCE OF SHORT WAVES ON THE DIPHTHERIA BACILLUS. E. HASCHE, Ztschr. f. Kinderh. **61**:506 (Dec. 22) 1939.

With poor cultural conditions injury to diphtheria bacilli is produced by a wavelength of 3.5 meters but not with a wavelength of 52 cm. With good cultural conditions neither wavelength has an effect.

Assuming that carriers provide poor cultural conditions, a trial of short wave therapy seems justified when ordinary methods of treatment fail.

SIEMSEN, Chicago.

STUDIES ON THE STABILITY OF THE SUSPENSION FOR THE AGGLUTINATION OF CORYNEBACTERIUM DIPHTHERIAE. C. H. HUANG and R. H. P. SIA, Chinese M. J. **57**:418 (May) 1940.

Corynebacterium diphtheriae is usually classified by either serologic or biologic typing. Anderson in 1931 gave a clinical classification of these organisms based on the severity of the condition. The gravis type was associated with severe toxic involvement, and the mitis type was associated with mild involvement. Some workers have doubted the accuracy of such a clinical classification. Huang and Sia sought to overcome the objections in the classification by getting a uniform suspension of these strains for agglutination.

A method is suggested which makes mass typing possible. The granular and spontaneous agglutinating strain may be made stable for specific agglutination if a concentrated solution of electrolyte is added. With the gravis form the growth must be on Loeffler's serum slope followed by suspension in one-fourth normal concentration of sodium chloride solution if a stable suspension is to be obtained.

NEFF, Kansas City, Mo.

INVOLVEMENT OF THE NERVOUS SYSTEM IN MUMPS. I. SNAPPER, Chinese M. J. **58**:79 (July) 1940.

A boy of 6 years, sick for two days with parotitis, had herpes zoster on the right side of the chest, with intolerable pain, and cramps in the calves of both legs. Headache and pain in the leg indicated involvement of the nervous system; the absence of knee jerks and the low biceps and triceps reflexes could best be explained by the meningoradiculitis, because of marked lymphocytosis of the cerebrospinal fluid. Herpes zoster, rarely associated with mumps or with meningoradiculitis, was probably due to involvement of the medulla or to an inflammation of an intervertebral ganglion.

Snapper states that the nervous system may be affected in many if not all cases of mumps. He emphasizes the fact that the mumps virus invades the central nervous system more constantly than the testicles. Invasion of the testicles occurs seldom in children. Some writers are of the opinion that mumps, like rabies, must be considered first a disease of the nervous system and only secondarily a localized process in the salivary glands. Lumbar puncture may disclose the existence of meningitis.

NEFF, Kansas City, Mo.

A Note on White Blood Cell Counts in Whooping Cough. C. T. Ch'in, Chinese M. J. **58**:98 (July) 1940.

The author's studies come from the pediatric department of Cheloo University Medical School in Tsinan, China.

Tables are given of total leukocyte counts for 266 patients with pertussis, grouped in various age periods, with the percentage and absolute number of lymphocytes and neutrophils for each age group. The rate of elevation in young infants was not so marked as in older children.

Leukocytosis was found in 96 per cent of cases and lymphocytosis in about the same percentage. These were greatest in the late catarrhal or active paroxysmal stage.

Neff, Kansas City, Mo.

Weltmann's Coagulation Band Reaction of the Cerebrospinal Fluid in Heine-Medin Disease. T. Kasue, I. Hosohara, H. Wada and K. Hirose, Acta pædiat. japon. **46**:643 (June) 1940.

In 37 cases of polioencephalitis in children the authors studied the coagulation band reaction of the cerebrospinal fluid by the Mori-Soya modification of Weltmann's method. It was found that during the first three weeks of the disease the reaction was strongly positive and that it did not become entirely normal until nine weeks later. No definite correlation was found between the positive reaction and the other data on the spinal fluid, such as the cell count, the protein content or the globulin reaction.

Kato, Chicago.

Vitamin B_1 Content of Spinal Fluid in Epidemic Poliomyelitis. F. Mori, Acta pædiat. japon. **46**:721 (June) 1940.

In 38 cases of epidemic infantile paralysis the author made quantitative estimations of the vitamin B_1 content of the cerebrospinal fluid by the improved thiochrome method and found the concentration of this vitamin to be generally diminished.

Kato, Chicago.

Tryptophane Content of the Cerebrospinal Fluid in Epidemic Polioencephalitis. S. Takasu and I. Gammo, Acta pædiat. japon. **46**:822 (July) 1940.

The author examined the tryptophane content of the cerebrospinal fluid in 20 cases of epidemic polioencephalitis and found it to be below 1 mg. per hundred cubic centimeters, or entirely within the normal limits.

Kato, Chicago.

The Tuberculin Test in Measles. H. Asano and S. Kikusima, Acta pædiat. japon. **46**:824 (July) 1940.

In 21 patients with positive tuberculin (intracutaneous) reactions, the effect of measles on the reaction was examined, two dilutions (1:100 and 1:2,000) being used. In 17 patients the reaction became negative, mostly during the six to nine day period of the attack of measles, and there was a return to the premeasles degree of reactivity on from the twelfth to the sixteenth day. In the remaining 4 children, however, no effect of measles on the tuberculin reaction was observed.

Kato, Chicago.

The Effect of Serum Therapy in Diphtheria. Von Bie, Acta med. Scandinav. **103**:201, 1940.

This is an analysis of the cases of 15,000 patients with diphtheria treated in the author's service. The serum was administered as soon as the diagnosis was

made and was given in one or occasionally in two doses within twenty-four hours. The mortality rate was 0.05 per cent in patients with mild involvement, 2.9 per cent in those with moderate involvement and 21.4 per cent in those with severe involvement if one excludes the patients who died within twenty-four hours after admission. The greatest mortality occurred in the age group from 0 to 4 years and decreased gradually with increasing age. In the cases of severe diphtheria the mortality rate was lowest for those who were admitted to the hospital on the first or second day of the illness; this indicates the effectiveness of serum treatment if given early. The mortality was much higher among those patients who had foetor ex ore, periglandular edema, hemorrhagic tendencies or albuminuria than among those without these complication. One third of the deaths occurred within twenty-four hours after admission; fewer occurred on the second day, and the rest were evenly distributed up to the thirteenth day after admission.

KAJDI, Baltimore.

Acute Infectious Diseases

AN EVALUATION OF THE BRUCELLA OPSONOCYTOPHAGIC TEST. BOWMAN WISE, Am. J. M. Sc. **200**:520 (Oct.) 1940.

The author examines the limitations and the usefulness of the opsonocytophagic test as a diagnostic aid when brucellosis is suspected. In the tests both the laboratory strain of Brucella suis, obtained from Huddleson, and the encapsulated strain isolated from a patient with Hodgkin's disease were used. The usual range of the brucella opsonocytophagic index for normal persons, as expressed by the index number, is from 0 to 30. A positive index is specific; that is, the blood cells of a person with a positive index do not phagocytose other types of organisms to any considerable degree. There is, however, a significant difference in the phagocytosis of the nonencapsulated and the encapsulated strains of brucella organisms. The brucella opsonocytophagic index has its greatest usefulness in indicating contact with brucella organisms; it is not diagnostic of active brucella infection and may be negative even when active infection exists.

HENSKE, Omaha.

TETANUS TOXOID IMMUNIZATION IN THE UNITED STATES NAVY. W. W. HILL, Ann. Int. Med. **14**:565 (Oct.) 1940.

Though this paper deals with the use of tetanus toxoid in the United States Navy, this summary of experience should be of interest to all pediatricians. Toxoid has been used in the Navy since 1934; groups of volunteers were used first. Reactions to properly prepared toxoid have been minor and infrequent. No case of tetanus has yet been reported in the group of over 3,400 persons who have been immunized.

At present the procedure is to give the toxoid intramuscularly, the two basic injections being given eight weeks apart. An injection is given with each injury, and one injection should probably be given each four years to maintain immunity at a high level.

GARD, Galveston, Texas.

OXYURIS INFESTATION. J. I. WARING, Arch. Pediat. **57**:615 (Oct.) 1940.

Use of the new type of swab made from cellophane has accounted for the great increase in the number of oxyuris infections diagnosed.

The most promising form of treatment is the use of tablets of gentian violet with a water-soluble coating. The dose for children is 10 mg. a day for each year of apparent age. Treatment is devised to cover the life cycle of the worm, which requires fourteen to twenty-one days.

ORR, Buffalo.

THE PATHOLOGICAL ASPECTS OF RHEUMATIC FEVER. CLARENCE E. DE LA CHAPELLE, Bull. New York Acad. Med. **16**:659 (Nov.) 1940.

The inflammatory lesion in rheumatic fever is primarily of two types, namely, exudative and proliferative. These are not sharply defined and vary somewhat with the organ involved. The initial lesion, pathologists now agree, originates in the supportive structures and the mesenchymal ground substance of the involved organs or tissues. The response to this injury includes edematous swelling of the collagen and elastic fibers with central necrosis accompanied by infiltration of a substance, probably fibrin. Edema then appears in the surrounding tissues, either widespread (in the inflamed joint) or local (subcutaneous nodule).

The initial reactions are mainly exudative. Later proliferating cells appear in the areas of altered collagen.

The gross and histologic changes involved in the various structures subject to attack are discussed in detail. Of particular interest in this connection are the pathologic changes in the heart, since carditis is the chief visceral manifestation. The myocardium and the valves are the structures involved in the majority of instances, the pericardium more rarely. The more severe the rheumatic inflammation, the greater the anatomic distribution. The primary inflammation is in the valve substance, with secondary changes in the surface epithelium (vegetations). Some persons consider the first lesion as endothelial.

The mitral and aortic valves are the most commonly involved. At the line of closure of the leaflets are small, firm, gray or pinkish verrucae. These are denuded of epithelium, and where they meet connective tissue various pathologic changes may be seen.

The various stages of the healing process are described. JAHR, Omaha.

EXPERIMENTAL BASIS OF CHEMOTHERAPY IN THE TREATMENT OF BACTERIAL INFECTIONS. E. K. MARSHALL JR., Bull. New York Acad. Med. **16**:723 (Dec.) 1940.

This is a comprehensive résumé of some of the outstanding experimental investigations on sulfanilamide and its derivatives. Experiments in vivo and in vitro on the toxic, bacteriostatic and bactericidal properties of the different compounds are reviewed, mainly from the point of view of their clinical application.

JAHR, Omaha.

THE CLINICAL USE OF SULFANILAMIDE AND ITS DERIVATIVES IN THE TREATMENT AND PROPHYLAXIS OF CERTAIN INFECTIONS. PERRIN H. LONG, Bull. New York Acad. Med. **16**:732 (Dec.) 1940.

This is an excellent digest of the present knowledge of sulfanilamide and its various derivatives, with emphasis on their clinical use in the treatment of bacterial diseases. This article must be read in the original if one is to benefit from the vast store of information contained therein. JAHR, Omaha.

"BILIOUS HEMOGLOBINURIC FEVER" AND ITS POSSIBLE RELATIONS TO FAMILIAL HEMOLYTIC CONSTITUTION. E. CORREA DE AZEVEDO, Arch. de pediat. **12**:35 (Sept.) 1940.

The author reports a case of "fiebre biliosa hemoglobinurica," or blackwater fever, in a 4 year old Negro child. There was first an attack of malaria, with acute onset. Treatment with quinine and quinine derivatives was begun, for blood films showed Plasmodium vivax. The patient died eight days after onset of the malady, with the symptoms of blackwater fever (constant vomiting, high fever and intense hemoglobinuria without hematuria).

The author then makes a thorough study of this disease and what he calls the "hemolytic constitution." He expresses the belief that the principal cause of this disease is toxic (quinine?); he considers quinine and its derivatives as a "powder

train" between the protozoan infection and the inherent fragility of the patient's red cells. Careful investigation disclosed lowered resistance of the red cells in the parents of the child in the case reported. He strongly advises such an investigation before the institution of quinine treatment. SOTO, Habana, Cuba.

Chronic Infectious Diseases

CONGENITAL SYPHILIS: II. COMPARISON OF TREATMENT WITH ACETARSONE AND OTHER ARSENICALS. R. A. LYON and F. C. O'NEIL, J. Pediat. **15**:19 (July) 1939.

Lyon and O'Neil summarize their study as follows: "Acetarsone and mercury inunctions were administered to a group of 53 children for periods of twelve to fifty-four months. These patients received an average of 7.5 courses over an average of a twenty-six-month period. [One complete course of treatment consisted of acetarsone administered for seven weeks and of mercury inunction for four weeks.]

"The results are statistically much better in younger children. In 10 of 15 (66.7 per cent) under 2 years of age the serologic tests were negative after one year of treatment; in 4 (26.7 per cent) the tests were positive, but there were no symptoms; in 1 (6.7 per cent) the test was positive and active lesions persisted. In only 13 (34.2 per cent) of 38 children between 2 and 15 years of age were the serologic tests negative after one year of treatment; in 21 (55.3 per cent) the serologic tests were positive, but symptoms or signs were absent, and in 4 (10.5 per cent), both positive serologic tests and symptoms or scars were present.

"The treatment with acetarsone has been compared with other forms of arsenic. Negative serologic tests and freedom from symptoms were obtained in approximately 67 per cent of 15 infants less than 2 years of age with acetarsone and in 79 per cent of 19 infants treated with sulpharsphenamine and neoarsphenamine. In older age groups, 34 per cent made good progress with acetarsone and 21 per cent with other arsenicals. These differences do not appear to be statistically significant." RAUH, Cincinnati.

DIAGNOSIS AND TREATMENT OF CONGENITAL OR PRENATAL SYPHILIS. JOHN H. STOKES and NORMAN R. INGRAHAM JR., M. Clin. North America **23**:1575 (Nov.) 1939.

There is no recognized standard therapy for congenital syphilis. The following basic principles may, however, be helpful:

1. Treatment should be begun only when the presence of the disease in the infant is established.

2. There is no adequate substitute for injection therapy in appropriate dosage.

3. No infant is too small or too young to receive treatment. The initial doses must be small, particularly in the presence of manifest disease, since therapeutic shock and therapeutic paradox may permanently damage the infant if too vigorous treatment is used at the start. It is seldom desirable to begin treatment with the arsenicals. It is safer to give a preparatory course of heavy metal, and even this should be given in not more than one half to one quarter of the maximum dose, calculated by weight, for the first ten to fourteen days.

4. Treatment should be continued without a rest interval and in alternating courses of arsenical and heavy metal (unless bismuth arsphenamine sulfonate is employed) for approximately one year.

The serologic findings during the first few weeks of life present apparent inconsistencies, which must be carefully considered in making a diagnosis of syphilis. For instance, 20 per cent of the offspring of syphilitic mothers who are "seropositive" at birth will on adequate follow-up never be shown to have syphilis. Con-

versely, hardly more than 40 per cent of infants subsequently proved to have syphilis will be seropositive at the time of birth. The majority, however, will have become seropositive in the course of one or two months. It is during these first few weeks of life, in the period of serologic uncertainty, that roentgenograms of the long bones may give valuable information.

In the diagnosis of tardive prenatal syphilis, clinical acumen and "the index of suspicion" have a most important place. A list of stigmas to be used as blotter reminders of what to look for in every patient examined should be a part of the mental equipment of the examiner. Among these "suspicion arousers" are: interstitial keratitis, hutchinsonian incisors, mulberry molars, deafness referable to the eighth nerve, saber tibia, periostitis, epiphysitis, osteochondritis and splenomegaly before the fourth month.

The diagnostic and therapeutic procedures outlined are illustrated in this paper by case histories and comment. Problems presented by the pregnant woman with syphilis are similarly handled.

EUGENE H. SMITH, Ogden, Utah.

ANOMALIES IN THE TUBERCULOUS REACTION IN THE CHILD. J. P. CERECEDA and J. M. RIVERA, Rev. chilena de pediat. **10**:544 (Sept.) 1939.

The authors find that infants who present evidences of constitutional diathesis and neurolabile subjects present an increasing sensitivity to tuberculin. Even small quantities are likely to produce severe reactions. These reactions are due to an excessive liberation of toxins against which these subjects have no adequate defense.

Injections of tuberculin should be used with great precaution in the treatment of these subjects, and at first in minute doses.

SCHLUTZ, Chicago.

CONGENITAL TUBERCULOSIS. ERWIN KEYSER, Kinderärztl. Praxis **11**:284 (Sept.) 1940.

A case of congenital tuberculosis is reported. Macroscopically the placenta was free from evidences of tuberculosis. Fever (temperature 101 F.) developed in the mature, healthy-looking newborn infant and was unexplained until roentgenograms were made. These showed bilateral disseminated infiltrations in both lungs. The tuberculin reaction was negative, but cultures of washings from the stomach were positive. When the infant was 34 days old he became cyanotic and dyspneic and died. Keyser believes that all cases of congenital tuberculosis are similar. No primary complex can be demonstrated in any of them. He concludes that infection through the blood stream or aspiration of amniotic fluid containing bacilli is the mode of infection.

HEYMANN, Cleveland.

TEN YEARS' EXPERIENCE OF BCG VACCINATION AT GOTHENBURG. H. ANDERSON and H. BELFRAGE, Acta pædiat. **26**:1, 1939.

Since 1927, vaccination with BCG has been practiced in Göteborg according to principles laid down by Wallgren. The vaccine (0.05 mg.) is administered intracutaneously. In all instances freedom from tuberculosis is rigorously demonstrated before vaccination; the inoculated persons are observed for six weeks after the procedure in order that the development of allergy can be confirmed. Up to the end of 1937 the number of children so vaccinated was 1,069. During the winter and spring of 1939, 905 of these children (85 per cent) were submitted to follow-up. The details of the investigation will be passed over. The concluding paragraph of the paper runs: "Thus among the whole of the material investigated only two cases of transient tuberculous disease occurred and no death took place from tuberculosis, whereas among the 'control materials,' which amounts to a very small percentage of the material investigated, there occurred 5 deaths and a number of cases of

tuberculous disease. Further, the investigation shows that a positive tuberculin reaction may be present for as long as 10 years after the BCG-vaccination even in children that have not been exposed to infection, which implies that the protection against tuberculosis the BCG-vaccination is intended to provide may persist in certain cases for fully 10 years. Thus the investigation made has, in our opinion, furnished still further support to the view we have held for some years that in the BCG-vaccination we possess a powerful preventive aid against tuberculosis. It is also our intention to strive for a more extensive application of the BCG-vaccination, especially among young adults in danger of tuberculous infection."

McCUNE, New York.

Diseases of Blood, Heart and Blood Vessels and Spleen

STUDIES ON THE AURICULOVENTRICULAR CONDUCTION TIME OF NORMAL CHILDREN AND OF RHEUMATIC CHILDREN WITHOUT SIGNS OF RHEUMATIC ACTIVITY. G. REYERSBACH and A. G. KUTTNER, Am. Heart J. **20**:573 (Nov.) 1940.

In a study of the electrocardiograms of 150 normal girls, varying in age from 6 to 16 years, prolonged auriculoventricular conduction time was found in 8 instances, or practically 5 per cent. In a group of 140 children with rheumatism who had no detectable signs of rheumatic activity and no demonstrable evidence of organic heart disease, the incidence of prolonged ariculoventricular conduction time was 5.7 per cent, practically the same as that for the normal children. Spontaneous variations in the PR interval occurred in the electrocardiograms of both the normal children and those with rheumatism. The clinical significance of an increase or decrease of the PR interval for children with rheumatism remains doubtful.

GIBSON, Chicago.

THE TETRALOGY OF EISENMENGER. O. SAPHIR and M. LEV, Am. Heart J. **21**:31 (Jan.) 1941.

The authors report a case of the tetralogy of Eisenmenger. This complex differs from the tetralogy of Fallot in that there is dilatation, rather than stenosis, of the pulmonary artery. The clinical differentiation of these conditions is discussed, and a new theory of transposition is presented to explain the occurrence of this anomaly.

GIBSON, Chicago.

TREATMENT OF CONGESTIVE HEART FAILURE WITH AN ORALLY ADMINISTERED MERCURIAL DIURETIC. R. C. BATTERMAN, A. C. DeGRAFF and O. A. ROSE, Am. Heart J. **21**:99 (Jan.) 1941.

Salyrgan-theophylline administered orally in the form of enteric-coated tablets in doses equivalent to 150 mg. of mercury is an effective and safe diuretic.

The diuresis not only is slower in onset but is more prolonged than that obtained with parenterally administered mercurial preparations.

The diuretic effect is less pronounced than that produced by the various parenterally administered mercurial preparations but greater than that obtained with the use of suppositories.

GIBSON, Chicago. [FROM AUTHORS' SUMMARY]

A MULTIPLE ANOMALY OF THE HUMAN HEART AND PULMONARY VEINS. W. J. ATKINSON JR., J. L. DEAN, E. H. KINNERDALL and C. J. LAMBERTSEN, Anat. Rec. **78**:383 (Nov. 25) 1940.

The two pulmonary veins opened into the superior vena cava, and there was a defect in the septum above the fossa ovalis. This is apparently a rare anomaly.

SNELLING, Toronto, Canada.

IRON METABOLISM AND ITS RELATIONSHIP TO ANEMIA AND THERAPY. WILLIS M. FOWLER and ADELAIDE P. BAKER, Ann. Int. Med. **14**:378 (Sept.) 1940.

Soluble and insoluble preparations of iron were used in this study of hypochronic, iron deficiency anemias. The soluble salts of iron, particularly the ferrous salts, had the greatest therapeutic value. Balance studies indicated that satisfactory increases in hemoglobin resulted from considerably smaller amounts of iron than had been generally employed, but this does not imply that larger doses are never indicated. The same amount of iron was not equally effective for all patients. Hemoglobin was formed more rapidly when large amounts of iron were available, either because of a greater ease of synthesis or because of an additional stimulating effect on the formation of hemoglobin.

READING, Galveston, Texas.

THE INCIDENCE OF THE FOUR MAIN BLOOD GROUPS IN RHEUMATIC HEART DISEASE. G. R. MAXTED, Arch. Dis. Childhood **15**:181 (Sept.) 1940.

The blood groups of 200 patients with rheumatic heart disease have been determined. The distribution of the blood groups does not differ from that in the general population.

KELLY, Milwaukee.

GAUCHER'S DISEASE: DIAGNOSIS BY STERNAL PUNCTURE AND IMPROVEMENT FOLLOWING SPLENECTOMY. J. N. MARSHALL CHALMERS, Arch. Dis. Childhood **15**:230 (Dec.) 1940.

The case of a 9 year old Jewish boy with Gaucher's disease is reported. Diagnosis was effected by sternal puncture. There was great clinical improvement following splenectomy. Chemical analysis showed that crude cerebroside formed approximately 4 per cent of the wet weight of the spleen. This material, when purified, was shown to have the physical and chemical characteristics of kerasin.

KELLY, Milwaukee.

STREPTOCOCCAL PERICARDITIS IN INFANCY: A REPORT OF TWO CASES. A. G. RUTTER, New Zealand M. J. **39**:197 (Aug.) 1940.

Two cases of streptococcic pericarditis in infants are reported. Twin premature children apparently contracted their streptococcic infections from the mother, who had puerperal fever. The mode of transfer was undetermined. One child died, and the other recovered. Both had been breast fed.

WEIGAND, Indianapolis.

THE CHRONIC ULCERATIVE-VEGETATIVE FORM OF ENDOCARDITIS. A. SEGERS, J. L. MONTSERRAT, M. E. DIAZ and A. RUSSO, Arch. argent. de pediat. **11**:147 (Feb.) 1939.

Ulcerative-vegetative endocarditis is a rare disease in infancy and especially in the first decade of life. The acute and subacute forms are more common than the chronic.

Chronic ulcerative-vegetative endocarditis, or the so-called disease of Jaccoud-Osler-Schottmüller, has definite characteristics and typical pathologic conditions which identify it as an independent disease entity. Anatomically there are ulceration and vegetation of the cardiac structures. The blood cultures usually reveal Streptococcus viridans.

The chronic forms of the disease in infancy and early childhood are uniformly fatal, and the prognosis is also extremely poor with the acute and subacute forms. Occasionally a patient recovers from the acute or the subacute form of the disease.

SCHLUTZ, Chicago.

TOTAL SITUS INVERSUS VISCERUM WITH CONGENITAL HEART DISEASE. F. PECORELLA, Pediatria **47**:714 (Aug.) 1939.

The case of a 3 year old chlid with true complete situs inversus viscerum who also showed the picture of Roger's disease is presented. The mother was afflicted with epidemic cerebrospinal meningitis at the second month of pregnancy, and the author feels that this may have been an etiologic factor in the situs inversus.

MARTOCCIO, Utica, N. Y.

THE HEART OF THE IMMATURE INFANT; ELECTROCARDIOGRAPHIC AND TELEROENTGENOGRAPHIC STUDIES AND ANATOMIC MEASUREMENTS. G. GUASSARDO, Riv. di clin. pediat. **38**:321 (June) 1940.

The electrocardiogram of the immature infant characteristically shows right-sided predominance and sinal arrhythmia. On anatomic measurements, the left side of the heart of the immature infant is slightly larger than the right, but relatively much less larger than in the adult heart.

HIGGINS, Boston.

CONGENITAL LESIONS OF THE HEART AS A CAUSE OF SUDDEN DEATH. W. MUNCK, Deutsche Ztschr. f. d. ges. gerichtl. Med. **32**:531, 1940.

Statistics concerning congenital cardiac defects are difficult to compile because of the differences in criteria used in evaluating anomalies. Pott found in a group of 30,000 children 95 under 10 years of age with congenital cardiac changes. In 1931 Berblinger found that 50 per cent of all children under 1 year and 33 per cent of adults had patent foramen ovale. When patent foramen ovale is classed as a congenital anomaly, therefore, the incidence of congenital heart disease is unduly high in proportion to its fatal outcome.

Munck presents the following statistics of 3,988 autopsies at the Medicolegal Institute of Copenhagen, Denmark. Of the 1,092 sudden deaths, 352 were those of children in the first year of life. Of these deaths, only 8 were attributable to congenital heart disease: 6 of the children who died were boys and 2, girls. The youngest was 3 days and the oldest 10.5 months old. There was a patent foramen ovale in every one of the bodies. Four hearts had large septal defects; 2 showed marked cardiac hypertrophy; 1, an aortic, and 1, a pulmonic, stenosis; 1, an atresia of the tricuspid orifice, and 1, a mirror image of this condition in atresia of the mitral orifice. One baby had chronic aortic and mitral endocarditis. The most unusual defect was an extra-auricular common channel for the pulmonary veins. The drainage was downward through the diaphragm and into the portal vein.

GEORGE J. RUKSTINAT. [ARCH. PATH.]

HEMOLYTIC ANEMIA WITH ERYTHROBLASTEMIA—A REPORT OF THREE CASES SEEN IN CHINESE INFANTS. C. Y. WANG and F. Y. KHOO, Chinese M. J. **58**:177 (Aug.) 1940.

Three infants aged 17, 8 and 2 months respectively had anemia with erythroblastosis, reticulocytosis, leukocytosis, increased urobilin in the stools and hyperplastic changes in the skull. The condition of the first infant corresponded to the syndrome formerly known as von Jaksch's anemia, and prompt recovery with disappearance of nucleated red cells was obtained by administration of ferrous sulfate solution.

The other cases ended fatally; in 1 the condition resembled Cooley's anemia, and in the other, erythroblastosis foetalis.

NEFF, Kansas City, Mo.

SOME CASES OF PRECORDIAL SOUNDS, AUDIBLE AT A DISTANCE. JØRGEN FROST and JENS BING, Acta med. Scandinav. **105**:411, 1940.

After a survey of the literature, 3 cases in which there were precordial sounds, audible at a distance and due to systolic or diastolic extra sounds, are reported.

In the first case no other abnormality was found to explain the sounds. In the second case there was spontaneous pneumothorax of the left side and in the third pulmonary tuberculosis with artificial pneumothorax of the left side. Characteristically, the sounds were heard when the patients were lying on the left side; when auscultation was performed while the patient was lying before the fluoroscopic screen, it was observed that the sound was heard at the exact moment that the heart, during its movements, touched the thoracic wall.

KAJDI, Baltimore.

Diseases of Nose, Throat and Ear

SULFANILAMIDE IN TREATMENT OF ACUTE INFECTION OF THE EAR AND OF THE MASTOID IN INFANTS AND IN CHILDREN: QUANTITATIVE STUDY OF SEVENTEEN CASES. HOWARD M. HEBBLE, Arch. Otolaryng. **31**:808 (May) 1940.

Conclusions in the study of the treatment with sulfanilamide of purulent aural infections characteristic of mastoid involvement in children are presented, and 17 cases of purulent middle ear infection indicating mastoid involvement and so treated are reviewed. Of note is the conclusion that patients showed a generally poor response to conservative medical treatment, including the use of sulfanilamide. The fact that the drug does mask symptoms in the presence of intracranial complications should be borne in mind but should not necessarily be considered a contraindication to its use.

GREENWOOD, Chicago.

PYOGENIC GRANULOMA OF THE NASAL FOSSA. IRA FRANK and MARGERY BLAHD, Arch. Otolaryng. **31**:919 (June) 1940.

Identification of bleeding polyps of the nasal fossa with granuloma pyogenicum by comparison of clinical and histologic characteristics of the lesions is discussed, and 5 illustrative cases are presented.

GREENWOOD, Chicago.

PSEUDOXANTHOMATOUS TUMOR OF THE MASTOID: RÉSUMÉ OF LIPOIDOSES. C. H. MCCASKEY, Arch. Otolaryng. **31**:938 (June) 1940.

The author describes the condition appearing as hemangioblastoma with pseudoxanthomatous change and discusses current knowledge relative to those conditions in which there is some underlying disturbance of lipoid metabolism, namely, the lipoidoses.

GREENWOOD, Chicago.

SUPPURATION OF THE PETROUS PYRAMID. ROBERT L. MOORHEAD, Arch. Otolaryng. **32**:845 (Nov.) 1940.

Three cases of suppuration of the petrous pyramid are presented. Typical symptoms are discussed. The relative value of the roentgenogram as a diagnostic aid is outlined, although sole reliance on the roentgenogram for decisive diagnosis is discouraged. It is agreed that no single method of treatment is applicable in all cases. Various therapeutic measures dependent on the clinical findings are outlined.

GREENWOOD, Chicago.

BACILLUS PROTEUS IN OTITIS MEDIA COMPLICATED BY MASTOIDITIS, MENINGITIS AND BACTEREMIA. ERWIN NETER and ROBERT A. CHAIT, Arch. Otolaryng. **32**:947 (Nov.) 1940.

The author presents a case of otitis media complicated by mastoiditis, meningitis and bacteremia. The presence of Bacillus proteus in the blood and the involved structures illustrates the potential pathogenicity of the micro-organism.

GREENWOOD, Chicago.

CONGENITAL ATRESIA OF POSTERIOR NARES. A. MANGIAROCINA, Arch. Otolaryng. **32**:1088 (Dec.) 1940.

The author reports the case of an 11 year old girl with congenital atresia of the posterior nares. The surgical procedure employed is presented in detail.

GREENWOOD, Chicago.

A TECHNIC FOR INSUFFLATING BENZEDRINE VAPOR IN CASES OF SINUSITIS IN INFANTS. HENRY A. MILLER, Arch. Otolaryng. **32**:1107 (Dec.) 1940.

The author presents the technic for insufflating benzedrine vapor in cases of sinusitis in infants. No undesirable reactions were noted, and marked symptomatic relief in 80 per cent of the cases was reported.

GREENWOOD, Chicago.

THROMBOSIS OF THE CAVERNOUS SINUS WITH RECOVERY. CLAUDE T. WOLFE and WILLIAM C. WOLFE, Arch. Otolaryng. **33**:81 (Jan.) 1941.

The authors present the first case of thrombosis of the cavernous sinus to appear in the literature in which sulfathiazole (2-[paraaminobenzenesulfonamido] thiazole) was used and complete recovery was thereby effected. Continued success with sulfathiazole is prophesied in combating staphylococcic infections, which are so often responsible for thrombosis of the cavernous sinus, a disease still attended by a high mortality.

GREENWOOD, Chicago.

TREATMENT OF PROFUSE HEMORRHAGE FOLLOWING TONSILLECTOMY; A NEW METHOD OF SUTURING. E. I. MATIS, Arch. Otolaryng. **33**:86 (Jan.) 1941.

The author describes an automatic instrument and attendant technic for suturing quickly and easily to stop bleeding following tonsillectomy. The advantages presented are the shortened suturing time of two minutes, the fact that the procedure, without assistance, necessitates the use of one hand only and the surety of suturing despite usual interferences, such as the patient's uneasiness, vomiting and obscurity caused by blood.

GREENWOOD, Chicago.

ACUTE UPPER RESPIRATORY INFECTIONS: REPORT OF LOCAL THERAPY OF 98 CASES IN CHILDREN. JOSEPH SCHWARTZMAN and IRVING WEINSTOCK, Arch. Pediat. **57**:778 (Dec.) 1940.

Ninety-eight children with infections of the upper respiratory tract were treated with mild nasal suction, nose drops, throat swabs and a combination of these methods. The results were inconclusive.

ORR, Buffalo.

INFLUENCE OF ADENOIDECTOMY ON THE CALCIUM-PHOSPHORUS-MAGNESIUM CONTENT OF THE BLOOD SERUM. C. CALABRESI, Arch. ital. di otol. **52**:273 (June) 1940.

Calabresi examined the blood serum of 28 children of both sexes, varying in age from 3 to 9 years and showing marked characteristics of adenoidism, in order to determine the influence of adenoidectomy on the content of calcium, phosphorus and magnesium. Examinations were made before operation and five days and twenty days afterward. The results of the examinations were: for calcium the average value before operation was 15.7 mg. per hundred cubic centimeters, five days afterward, 12.5 mg. and twenty days afterward, 11.5 mg.; for magnesium the figures were 3.5, 3 and 2.6 mg., respectively; inorganic phosphorus averaged 6.7, 5.2 and 5.4 mg. for the respective periods, and the averages for acid-soluble phosphorus were 8.5, 7.3 and 7.3 mg. The investigation thus reveals that the blood serum of children with adenoids contains larger amounts of the three elements than are found in that of normal children, while after adenoidectomy there occurs a decrease in the amounts of all three elements, with a tendency to approach normal percentages.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

MICROSCOPIC ANATOMY AND HISTOPHYSIOLOGY OF THE PALATINE TONSIL. G. CARLO and R. FRANCO, Arch. ital. di otol. **52**:280 (June) 1940.

Carlo and Franco studied the minute anatomy of the tonsils removed from 14 patients, who varied in age from 4 to 69 years. Three important points in the observations are emphasized: the penetration of the epithelial layer by the lymphoid tissue, the significance of the clear centers in the lymphatic nodules and the process of evolution of the tonsil. The penetration of the epithelial layer by the lymphoid tissue is always circumscribed, is most marked at the bottom of the crypts or around their mouths and is preceded by the penetration of the capillary papillae, in the connective tissue of which the lymphoid infiltration is established. This phenomenon is regarded as an expression of chronic local inflammation. Sometimes the groups of epithelial cells isolated by the penetration have the appearance of thymic corpuscles.

The clear centers in the lymphatic nodules were observed more frequently in patients over 20 years of age; in the hypertrophied tonsils mitosis, exclusively localized in the clear centers, was increased. The clear centers are regarded as true germinative centers. In both the nodules and the internodular lymphoid tissue microphages and evidences of destruction (from toxic action) were observed.

The process of evolution was constantly present in the tonsils of patients 12 years of age and onward, although signs of evolution, sometimes advanced, were observed in those of younger subjects and even in hypertrophied tonsils. Among the early signs of evolution are rarefaction of the lymphocytes in the internodular lymphoid tissue, thickening of the walls and reduction of the lumens of the arteries and hypertrophy of the reticulum of the nodules and its transformation into collagenous tissue. In addition, in patients between the twelfth and the twenty-seventh year of age there is "tumultuous" massive liquefaction of lymphocytes in the periphery of the tonsil. Because this process is occasionally observed in younger subjects, it is regarded as an accidental involution, similar to that occurring in the thymus. Pyknosis and fragmentation are characteristic at all ages, and, since this process is identical with that observed in the thymus, where it is a morphologic expression of endocrine activity, it may have a similar significance in the tonsil.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

Diseases of Lungs, Pleura and Mediastinum

PATHOGENESIS OF BRONCHIECTASIS. FELIX FLEISCHNER, Am. Rev. Tuberc. **42**:297 (Sept.) 1940.

The basic mechanism which underlies the development of any bronchiectasis is a disturbance of the self-cleansing capacity of the lung, which results in the retention of secretion and the obstruction of small bronchi. Atelectasis thereby develops in the pulmonary area served by these structures. The atelectatic rigidity and contraction of the tissues surrounding them exert a pathologic pull on the bronchial walls, and under the necessity of spatial adjustment in the unyielding thorax the bronchi become dilated. The dilatation at first is reversible, but later it becomes permanent if the intervening factors operate for a long time. The developed atelectasis further hampers removal of secretion and causes inefficient ventilation of the neighboring parenchyma.

This conception of the pathogenesis of bronchiectasis is interesting from the standpoint of the clinical background of the condition. If atelectasis is the first structural step in its development, the frequency with which this condition occurs during the course of the common types of infections of the respiratory tract, from youth to old age, assumes new importance. The pneumonias of childhood, influenzal pneumonia and the atelectatic paravertebral pneumonias of infancy may well

be the obscure forerunners of later chronic conditions. The simultaneous occurrence of chronic sinusitis and bronchiectasis may be explained as a result of the following factors: sinusitis, breathing by mouth, shallow breathing, insufficient respiratory change of the volume of the lung and predisposition to the development of atelectasis and bronchiectasis.

This idea of bronchiectatic disease, if proved, offers hope of greater success in the prophylaxis and the treatment of this condition. The training of all persons to breathe correctly from early childhood is of fundamental importance. In all acute infections of the respiratory tract, in every bronchostenosis, in every abdominal disease and operation, in every injury to the chest—in short, in all conditions which tend to produce atelectasis or to reduce ventilatory efficiency—every effort should be made to remove the disturbing agent and to restore complete reaeration and ventilation of the lung.

EUGENE H. SMITH, Ogden, Utah.

MYCOTIC INFECTIONS OF THE BRONCHO-PULMONARY TRACT. A. J. VADALA, Ann. Otol., Rhin. & Laryng. **49**:291 (June) 1940.

The author gives a comprehensive review of fungous infection of the bronchopulmonary tract. For clinical purposes the fungi invading the bronchopulmonary tract are conveniently classified into (1) yeastlike organisms, such as Cryptococcus, Oidium, Monilia and Saccharomyces and (2) filamentous forms, such as Actinomyces.

Discussing the general symptoms of mycotic infection of the lungs, the author says that the disease may run a mild course, with few symptoms, the clinical course resembling that of chronic bronchitis. These conditions frequently clear up without any complications. On the other hand, there is another type of the infection, which runs a malignant course. The patient loses weight and has a cough with hemoptysis, and the sputum frequently has a nauseating foul odor, which is helpful in making the diagnosis. The physical signs and character of the disease resemble those of tuberculosis. Examination of the chest may show rales and dull areas. Roentgen signs cannot be differentiated from those present in cases of tuberculosis. Final diagnosis depends on aspirating some exudate with the bronchoscope and making cultures of the material on specially prepared mediums.

Infection with the various types of fungus is discussed at some length, and the author describes signs, distribution, diagnosis and treatment. The iodides are extremely effective in the treatment of many types of fungous infection, but because of the difficulty in making a differential diagnosis between these and tuberculosis, the reader is warned to be sure of the diagnosis before giving the iodides. Specific therapy and nonspecific therapy have been used, with conflicting reports resulting. The former, however, is a help in diagnosis in some cases.

The use of irradiation, combined with either surgical treatment or the administration of iodides, is discussed in connection with actinomycoses. Various treatments for the various types are considered, and one gets a complete picture of the present day knowledge of this troublesome infection. Full case reports of 10 patients are presented. M. V. MILLER, Philadelphia. [ARCH. OTOLARYNG.]

VEGETABLE FOREIGN BODY IN THE LUNG FOR A MONTH; SUCCESSFUL REMOVAL; RECOVERY COMPLICATED BY MEASLES. CLYDE E. HARNER, Arch. Otolaryng. **32**:951 (Nov.) 1940.

Reported here is the case of a 21 month old boy in whose right main bronchus a vegetable foreign body remained for one month before it was discovered and successfully removed.

GREENWOOD, Chicago.

FURTHER EXPERIENCES WITH SULFAPYRIDINE IN THE PNEUMONIAS OF INFANCY AND CHILDHOOD. JEROME S. LEOPOLD and IRWIN PHILIP SOBEL, Arch. Pediat. **57**:710 (Nov.) 1940.

Fifty-six infants and children with pneumonia were treated with sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine). Of this group 45 per cent were under 2 years of age. There were no fatalities, and with the exception of occasional vomiting no toxic manifestations of the drug occurred.

The authors state that toxic manifestations may be avoided through a generous intake of fluids and a discontinuance of the drug after the patient has been afebrile for twenty-four to forty-eight hours.

ORR, Buffalo.

TYPE I PNEUMOCOCCUS PNEUMONIA INVOLVING IDENTICAL LOBES IN IDENTICAL TWINS. LEWIS JACOBS and JACOB SOBOL, Arch. Pediat. **57**:765 (Dec.) 1940.

The occurrence of this phenomenon in 8 month old Negro boys who were identical twins is reported.

ORR, Buffalo.

PULMONARY ABSCESS WITH FISTULA IN AN INFANT. A. WIEDERHOLD, Arch. d. Hosp. niños Roberto del Rio **9**:169 (Oct.) 1940.

A chronic pulmonary abscess in a child of 3 months drained spontaneously through the axilla. Roentgenograms are shown. Death occurred.

SANFORD, Chicago.

TREATMENT OF BRONCHIAL ASTHMA BY INJECTION OF THE PATIENT'S OWN BLOOD SERUM. G. TAMÁSI, Kinderärztl. Praxis **11**:248 (Aug.) 1940.

Eighty to 120 cc. of blood is taken from a patient during an attack of bronchial asthma. The blood is allowed to stand for twenty-four hours in a refrigerator, after which time the serum is prepared and 0.5 per cent phenol is added. Tamási injects this serum three times a week for from four to six weeks in increasing doses (0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 cc.), at first subcutaneously and later intramuscularly, into the same patient, after the acute attack has subsided. He has treated 8 children in this way, 5 of whom remained free from further attacks for one to two years. In 2 of the patients the condition improved, and in 1 it remained unchanged.

HEYMANN, Cleveland.

SULFAPYRIDINE IN PNEUMONIA. W. TRACHSLER, Med. Klin. **35**:1210 (Sept. 8) 1939.

The author's experience with sulfapyridine in 14 cases of lobar pneumonia at the Zurich Children's Hospital confirms the favorable results reported by American and English authors. He recommends a dosage of 1 Gm. per 10 Kg. of body weight per twenty-four hours, equally divided in two four hour doses, and a decreased dose on clinical improvement. No untoward manifestations were observed in the cases described.

SIEMSEN, Chicago.

THE THERAPY AND PROPHYLAXIS OF POSTOPERATIVE PULMONARY COMPLICATIONS WITH CHINFORTAN. E. WALLBRUCH, München. med. Wchnschr. **78**:828 (Aug. 2) 1940.

There is a high incidence of postoperative pulmonary complications in industrial areas. These are usually purulent bronchitis and bronchopneumonia resulting from a mixed infection with pneumococci and streptococci. Administration of chinfortan (a combination of quinine and sulfanilamide) seemed desirable. During six months 50 cases in which purulent expectoration and a high temperature persisted for two or three days after operation were observed; the patients were treated with chinfortan, with good results. A dose of 2 cc. twice daily usually

brought the temperature to normal in two days, with an associated improvement in the clinical symptoms. The subsequent course was uneventful, and there were no unpleasant side reactions.

Equally satisfactory was the preoperative administration of chinfortan to patients with chronic disease of the respiratory tract. Such patients received 2 cc. of chinfortan several days before and after the operation. No pulmonary complications occurred, which is in contrast to previous experience. Now patients without pulmonary conditions are given chinfortan the evening before and for several days after an operation. As a result no serious pulmonary complications have developed.

BRAHDY, Mount Vernon, N. Y.

PNEUMONIA DIAGNOSIS IN EARLY CHILDHOOD. II. C. FRIDERICHSEN, Acta pædiat. **27**:1, 1939.

In order to evaluate the absolute and the relative merits of several types of treatment, Friderichsen undertook the disheartening job of constructing yet another clinical classification of the various manifestations of pneumonia in early childhood. The data embraced the results of physical, roentgen, hematologic and bacteriologic examinations carried out systematically. Sixty-four patients less than 2 years of age were studied. Three main forms of pneumonia, with subgroups, were distinguished:

"I. The primitive form: a) hilufugal, b) miliary, c) primary abscess formation. These forms are characterized by a strong tendency to dissemination of the pneumonic process in the lung field.

"II. The transition forms: a) focal, b) marginal, c) partially lobar, d) lobar. These forms are characterized by a tendency to focal limitation of the processes, localized to different places in the lung. The tendency to form a focus must be considered an allergic process.

"III. The croupous pneumonia is typical of the quite mature form, which can be distinguished from the lobar transition form only by means of its clinical picture, as the X-ray photos of both these forms present the same shadow formation."

Bacteriologic evidence indicated that the pneumococcus was the causal agent in a high proportion of all cases, irrespective of the clinical character of the pneumonia; organisms of types VI, XIX and XXIII were those most frequently encountered in the cases of patients under 2 years of age. The hematologic findings were not novel. The sedimentation rate of the erythrocytes was found to be a more dependable basis on which to decide to let the child be up than the temperature of the body.

MCCUNE, New York.

A CASE OF PNEUMOTHORAX. B. VOLTAY, Orvosi hetil. **83**:982 (Nov. 11) 1939.

A 4 year old girl, after an attack of pneumonia, had empyema on the left side of the chest. After resection of two ribs the empyema healed in two months. The child was well after that, but after a violent fit of crying she became cyanotic, rapid respiration developed and she complained of shooting pains on the left side. She was brought back to the clinic three days later, and the roentgen examination showed complete pneumothorax on the left side and a decided displacement of the mediastinum toward the right. The removal of the air did not improve the situation for a long time; therefore a resection of another rib was necessary, after which the child quickly recovered. The cause of this pneumothorax was probably the rupture of the visceral pleura, which had grown together with the parietal pleura during the empyema.

GÖTTCHE, Budapest, Hungary.

TREATMENT OF PNEUMONIA IN EARLY INFANCY. C. FRIDERICHSEN, Acta pædiat. **26**:167, 1939.

The author's summary reads: "After serum treatment of 28 children, in whom the pneumonias were verified by X-ray, no difference in the mortality

was found in comparison with the control cases within the different pneumonias and age-classes. The intraperitoneal blood transfusion is a valuable therapeutic remedy in the treatment of acute primitive as well as of chronic and migrating pneumonias, and it is able to serve as substitute for intravenous blood transfusion during the first year of life. Forty-six children (21 of whom were below 2 years) with pneumonia, verified by x-ray and typing, were treated with sulfapyridine. Decrease of temperature ensued in 45 cases. One child died on account of complicating encephalitis with type VI. Sulfanilyl-aminopyridine is able to kill pneumococci in lung tissue and blood, but not in brain tissue, which is poor in lymph. In the treatment of pneumonias in early childhood sulfanilyl-aminopyridine is very superior to serum."

McCUNE, New York.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CARDIAC HYPERTROPHY CAUSED BY GLYCOGEN STORAGE DISEASE IN A FIFTEEN-YEAR-OLD BOY. W. ANTOPOL, E. P. BOAS, W. LEVISON and L. R. TUCHMAN, Am. Heart J. **20**:546 (Nov.) 1940.

The authors report the case of a 15 year old boy who had what they believe to be the cardiomegalic type of von Gierke's disease. Because practically all other reported cases have been those of infants, other possible diagnoses have been considered. A discussion of the relation of glycogen storage to so-called idiopathic hypertrophy of the heart is included.

GIBSON, Chicago.

CONGENITAL DIAPHRAGMATIC HERNIA: REPORT OF A SUCCESSFULLY OPERATED CASE. JOHN H. WILLARD, Am. J. Digest. Dis. **7**:447 (Nov.) 1940.

This is an excellent review of the literature, with a report of the case of a 12 year boy. The hernia occurred through the foramen of Bochdalek (hiatus pleuroperitonealis). Only 16 similar cases in which the abnormality occurred in a child under 15 years of age were found in the English literature.

The two main points to be stressed are: (1) Congenital diaphragmatic hernias in children are of serious prognostic significance. (2) Successful surgical repair may be accomplished even in young infants.

MORRISON, Savannah, Ga.

EFFECTS OF INJECTION OF EXTRACT OF YEAST ON GASTRIC SECRETION IN DOGS. EDWARD F. WILLIAMS JR., WILLIAM W. COX and THOMAS P. NASH JR., Am. J. Physiol. **131**:378 (Dec.) 1940.

A concentrated extract of fresh yeast has been prepared which when injected intramuscularly stimulates gastric secretion in a manner similar to that of histamine. The injection of 4.5 mg. of thiamine hydrochloride was without effect. While such tests as have been made suggest that the active principle of the yeast extract is not histamine, the evidence on this point must be considered as inconclusive.

NOURSE, Cleveland.

A CASE OF ATRESIA OF THE ESOPHAGUS COMBINED WITH TRACHEO-ESOPHAGEAL FISTULA IN A 9-MM. HUMAN EMBRYO, AND ITS EMBRYOLOGICAL EXPLANATION. PETER GRUENWALD, Anat. Rec. **78**:293 (Nov. 25) 1940.

A 9 mm. human embryo displaying typical, well established features of the malformation is described.

SNELLING, Toronto, Canada.

SURGICAL ANASTOMOSES BETWEEN THE BILIARY AND INTESTINAL TRACTS OF CHILDREN. WILLIAM E. LADD and ROBERT E. GROSS, Ann. Surg. **112**:51 (July) 1940.

The purpose of this paper is to summarize the late clinical status of all patients with a congenital abnormality of the bile passages treated surgically by joining the

biliary and the intestinal system. Ten patients survived anastomosis. They ranged in age from 1 month to 5 years.

The findings are summarized as follows:

1. In every case there was clinical evidence that the alimentary system was functioning normally.

2. In 1 case there was chronic recurring infection of the biliary tract. In the other 9 cases jaundice disappeared within a few weeks after operation and did not recur.

3. All the children had extraordinary powers of regenerating liver substance. Children do not die of cirrhosis in these circumstances, as was formerly believed.

4. All children showed normal physical development following operation.

5. No child showed the slightest clinical evidence of uremia, oliguria, circulatory collapse or death after the sudden release of dammed-up bile from the biliary passages.

6. While the union of the bile ducts or the gallbladder with the stomach or the duodenum causes some distortion of the gastric antrum, it does not give rise to anorexia, nausea or vomiting.

BANTIN, Omaha.

CONGENITAL PYLORIC STENOSIS. DAVID E. ROBERTSON, Ann. Surg. **112**:678 (Oct.) 1940.

Dr. Robertson has found that pyloric stenosis occurs most frequently in first-born children and more often in males. The symptoms are occasionally observed within a few hours after birth.

The author expresses the belief that the condition is best treated by operation. He advises preoperative measures to combat dehydration and acidosis if they are present. Ethyl chloride and ether or ether alone seems to be the anesthetic of choice. A new type of incision is advised, and the operative procedure is given in detail. The incision is made parallel to the right costal margin and about one-half inch (1.3 cm.) below it. Feeding is started four hours after operation.

BANTIN, Omaha.

SURGICAL EMERGENCIES DURING CHILDHOOD CAUSED BY MECKEL'S DIVERTICULUM. LAWRENCE CHAFFIN, Ann. Surg. **113**:47 (Jan.) 1941.

Meckel's diverticulum represents a remnant of the omphalomesenteric duct, through which nourishment passes from the yolk sac to the embryo; generally, the structure has vanished by the time of the child's birth. Whenever it persists, it becomes a menace to health.

Its incidence as disclosed by autopsy is around 2 per cent, and it is present more often in males. In 17 of the author's series of 19 cases the patient was a boy.

The surgeon should never overlook a diverticulum as the possible source of trouble whenever he is called on to treat an acute abdominal condition during childhood.

The author's cases illustrate the familiar complications of hemorrhage, ulceration, perforation, peritonitis, intussusception, volvulus, intestinal obstruction, umbilical sinus and umbilical fecal fistula.

Operation resulted in recovery in 12 cases and death in 7.

BANTIN, Omaha.

CHRONIC GASTRIC ULCER IN CHILDHOOD, TREATED SURGICALLY. G. B. LOGAN and WALTMAN WALTERS, Ann. Surg. **113**:260 (Feb.) 1941.

Chronic gastric ulcer is a comparatively rare disease in children. Thirty-four cases have been reported in children 14 years of age or younger. Of approximately 2,000 patients with chronic gastric ulcer at the Mayo Clinic from 1924 to 1939, only 1 was a child.

The etiology remains the same unsolved problem in childhood that it is in adult life.

The diagnosis is difficult because of the rarity of the disorder in children and the bizarre symptoms which it produces. "The most important single factor in the diagnosis is the realization that chronic peptic ulcer occurs in children." Chronic digestive disturbances, indefinite abdominal discomfort, anorexia, pain at night and vomiting should suggest the possibility of peptic ulcer. The roentgenologic picture is characteristic.

The authors review 15 cases from the literature and report 1 case in detail.

BANTIN, Omaha.

CONGENITAL ATRESIA OF THE PANCREATIC DUCT WITH CYSTIC FIBROSIS OF THE PANCREAS. ELLA H. OPPENHEIMER, Arch. Path. **29**:790 (June) 1940.

Dilatation of the acini and ducts of the pancreas, together with an increase of fibrous tissue, was the chief cause of gastrointestinal symptoms dating from birth in a white girl. The child had presented a feeding problem characterized by failure to gain weight, vomiting and steatorrhea. The usual respiratory changes found in these cases of purulent bronchitis and bronchopneumonia were present.

Histologically, this case is unusual because the author was able to demonstrate an atresia of the main pancreatic duct as the probable cause of the changes in the pancreas. In addition, there was squamous metaplasia of the bronchial epithelium to which the author ascribes the role of predisposing cause of the pulmonary infection.

APFELBACH, Denver.

APPLE THERAPY. IRA A. MANVILLE, Arch. Pediat. **57**:302 (May) 1940.

The subject is reviewed.

ORR, Buffalo.

ENTEROGENOUS CYST OF THE DUODENUM. JAMES B. GILLESPIE and J. C. THOMAS ROGERS, Arch. Pediat. **57**:652 (Oct.) 1940.

This condition was discovered in a boy 4½ years of age who was operated on because of jaundice and a mass in the abdomen.

ORR, Buffalo.

ACUTE ABDOMEN IN CHILDREN. SAMUEL GOLDBERG, Arch. Pediat. **57**:783 (Dec.) 1940.

The problem of acute surgical conditions of the abdomen is discussed.

ORR, Buffalo.

SOLITARY NONPARASITIC CYSTS OF THE LIVER IN CHILDREN. ALBERT H. MONTGOMERY, Arch. Surg. **41**:422 (Aug.) 1940.

Two cases of this rare condition are reported. Such cysts are rarely found in infants and young children. After reviewing the literature on this subject, the author comes to the conclusion that nonparasitic cysts of the liver are congenital and of biliary origin, perhaps arising from aberrant bile ducts which result in benign, cystic adenomas. Such cysts of the liver usually do not cause symptoms unless they become large enough to cause pressure symptoms or are palpable. Surgical removal is the treatment of choice when possible.

KAISER, Rochester, N. Y.

THE GASTROINTESTINAL RESPONSE OF CHILDREN TO TEST MEALS OF BARIUM AND PASTEURIZED, EVAPORATED, AND BASE-EXCHANGED MILKS. LAWRENCE REYNOLDS, ICIE G. MACY and HELEN J. SOUDERS, J. Pediat. **15**:1 (July) 1939.

This study was undertaken to determine the relation of gastrointestinal motility to milks of different curd tension. Pasteurized milk, evaporated milk and a

processed "base-exchanged" milk were used. The "base-exchanged" milk was specially treated by being passed through sodium-aluminum silicate (zeolite), during which process approximately 17 per cent of the calcium, 14 per cent of the phosphorus, 6 per cent of the chlorine and 32 per cent of the potassium were exchanged for an increase of 85 per cent in sodium and 7 per cent in magnesium. All the milk used was collected from the same herd of cows. Seven healthy children, aged 7 to 11 years, each of whom had been observed previously in a study of acid-base mineral balance and whose gastrointestinal motility patterns were known, served as subjects of serial roentgen studies on the orderly passage through the alimentary tract of test meals composed of 2 ounces (62.2 Gm.) of barium sulfate and 4 ounces (124.4 Gm.) of pasteurized milk, evaporated milk diluted 1:1 with water and base-exchanged milk. Roentgen examinations were made at frequent intervals until the meal had passed out of the stomach and at 24, 48 and 72-hour intervals after ingestion.

The authors report their observations as follows: "The average gastric emptying times for the 7 children were two hundred and twenty-seven, two hundred and fourteen and one hundred and ninety-three minutes, respectively, for pasteurized, evaporated and base-exchanged milks. The roentgenograms taken ten minutes after ingestion indicated that the soft curd milks began emptying from the stomach in much less time than the pasteurized milks; in 9 instances the soft curd milk had reached the duodenum and in 4 of these had entered the jejunum after ten minutes, while in only one exposure at the ten-minute interval had the pasteurized milk meal left the stomach." At the end of one hour after ingestion of the meals, the more rapid motility of the meals of soft curd milks was definite. After two to three hours the soft curd milks showed greater advancement through the intestinal tract, but the pasteurized milk meal made relatively greater progress during the interval between one and three hours after ingestion.

RAUH, Cincinnati.

CONGENITAL ATRESIA OF THE OESOPHAGUS. MILDRED I. EALING, Brit. M. J. **2**:83 (July 20) 1940.

A case of congenital atresia of the esophagus with autopsy is reported. The occurrence of this condition, which is relatively frequent in America, seems to have been more or less overlooked in England.

ROYSTER, University, Va.

PERITONITIS FROM THE COLON BACILLUS IN AN INFANT WITH LIPOID NEPHROSIS. AGUSTÍN CASTELLANOS, Arch. de med. inf. **9**:232 (Oct.-Dec.) 1940.

An organism of the Escherichi strain was recovered from the blood twenty-four hours after the onset of abdominal symptoms. Since there was no disturbance of the gastrointestinal tract, the author expresses the belief that the peritonitis was of hematogenous origin. In Cuba, as in the United States, the pneumococcus is the most frequent cause of peritonitis in cases of nephrosis. Treatment with sulfathiazole (2-[paraaminobenzenesulfonamido] thiazole) was effective.

SANFORD, Chicago.

SURGICAL TREATMENT OF ACUTE ABDOMINAL SYNDROME IN THE CHILD. RAUL M. DEL CAMPO, Bol. Inst. internac. am. de protec. a la infancia **13**:331 (Oct.) 1939.

The diagnosis and treatment of any acute abdominal syndrome in the child ought to be early.

1. When the diagnosis of appendicitis is sure, intervention must be immediate.

2. Nevertheless, there exist some abdominal processes with which it is better to await localization before instituting surgical treatment, e. g., pneumococcic peritonitis.

3. There are some intestinal intussusception processes in which radiologic or radiosurgical treatment gives excellent results.

4. Ether is the anesthetic best tolerated and is rapidly and easily eliminated. The local anesthetic procaine hydrochloride, 0.5 to 1 per cent, is convenient in many cases.

It is always necessary to have in mind the child's constitution. The anesthetic which is suitable for the normal child does not always suit children with neurolabile, spasmophilic or exudative conditions.

5. The care before and after operation must be intensified for the child.

6. One should give attention to postoperative hypothermia or hyperthermia, shock and the function of the kidneys.

7. One should keep in mind effective action of intravenous hypertonic salt solutions in cases of postoperative chloropenia, in cases of meteorism and above all in the presence of the frequent complication paralytic ileus.

FROM AUTHOR'S CONCLUSIONS.

USE OF VITAMIN C IN DISEASES OF THE LIVER. JOSÉ M. GONZÁLEZ GALVÁN, Rev. méd. latino-am. **15**:649 (March) 1940.

Patients with hemorrhages of the gastrointestinal tract, especially if these are accompanied with hepatic disease, should have large doses of vitamin C as a supplement to any other therapy employed. The diuretic effect of vitamin C is also of benefit in cases of ascites due to hepatic cirrhosis. Lesions of the oral, vulvar and anal mucous membranes, accompanied with hepatic insufficiency, responded favorably to vitamin C. Toxic hepatitis also responded to this vitamin. The author studied its effect on cutaneous pigmentation from various causes: scurvy, Addison's disease and certain forms of chloasma and the diseases of the liver. He attributes the beneficial action of vitamin C in these conditions to the resemblance between the chemical constitution of ascorbic acid and that of the adrenal hormone.

DWYER, Kansas City, Mo.

TWO CASES OF ACUTE INTESTINAL INTUSSUSCEPTION IN INFANTS UNDER SIX MONTHS OF AGE. MARIA PIAZZA-POLIAK, Lattante **11**:128 (April) 1940.

Two cases are reported of breast-fed infants with acute intussusception, operated on fourteen and eighteen hours after the onset of symptoms; both patients recovered. Enemas in both cases had failed to reduce the obstruction.

A plea is made for early operation, since the mortality among patients operated on during the first twenty-four hours is practically nil and among patients operated on after forty-eight hours is over 80 per cent.

HIGGINS, Boston.

TWO FURTHER CASES OF INTUSSUSCEPTION IN INFANTS. M. GIOSEFFI, Lattante **11**:133 (April) 1940.

Two cases of intussusception are reported. In the first, operation was successful. In the second, operation was not permitted; the intussusception reduced itself, only to recur within a month; again reduction occurred without surgical intervention. The child's recovery may be ascribed to the "vis medicatrix naturae."

In the 2 cases reported by Piazza-Poliak, the mothers, by their insistence in bringing the infants to the hospital in the face of other medical advice, probably saved the lives of their infants. In the first case reported by Gioseffi considerable pressure had to be brought to gain the parents' consent, especially since a consulting physician diagnosed the condition as dysentery.

The increased penetration of pediatrics into the smaller villages and the country, especially through government child protection bureaus, should aid in earlier and better diagnosis of such pediatric emergencies as intussusception.

HIGGINS, Boston.

PATHOLOGY AND THERAPY OF ALIMENTARY DISORDERS IN INFANCY. E. HAINISS, Orvosképzés **29**:490 (July) 1939.

Hainiss criticizes the present situation with regard to this question.

GÖTTCHE, Budapest, Hungary.

CATHEPSIN OF THE GASTRIC JUICE. SAMUEL BUCHS, Ann. pædiat. **156**:1 (Oct.) 1940.

The author has tried to give a satisfactory explanation for the digestion of protein in infants' stomachs in which the acidity of the gastric juice excludes a sufficient activity of pepsin. By experiments with the gastric juice of more than 80 children he was able to demonstrate the presence of a second active proteolytic enzyme, which has the following qualities:

(1) It splits genuine proteins into polypeptides. (2) It is found in the gastric juice of subjects of all ages. (3) It is most active when the p_H of the liquid is near 4.7 and (4) the temperature is near 60 C. (140 F.). (5) Its splitting action is increased by the addition of hydrogen sulfide, potassium cyanide and magnesium chloride. (6) It was possible to separate the ferment from pepsin to a certain degree by using the method of adsorption by cholesterol.

This gastric enzyme belongs to the group of Willstätter's cathepsins and to the large family of papainases.

Curdling of milk in the stomach is effected—if not by hydrochloric acid—by the pepsin-parachymosin, not by the cathepsin, of the gastric juice. There is no true chymosin either in infancy or in adult life.

AUTHOR'S SUMMARY.

THE TREATMENT OF "SUMMER DIARRHEA" WITH BACTERIOPHAGE. A. ECKSTEIN and I. DOČRAMACI, Ann. pædiat. **156**:65 (Jan.) 1941.

After several years' preliminary trial, the authors began to treat summer diarrhea of infants with bacteriophage. Observations during, as well as after, treatment showed that the degree of success of the therapy was related to the severity of the disease. In cases in which there was toxicity this method failed, while treatment with polyvalent antidysentery serum confirmed the good results previously reported. Treatment with bacteriophage in cases of serious or moderately serious disease proved to be superior to the usual medical therapy. The possibility of prophylaxis of summer diarrhea by bacteriophage is to be studied.

AUTHORS' SUMMARY.

THE ACTIVITY CURVES OF THE CATHEPSIN OF GASTRIC JUICE. E. FREUDENBERG, Ann. pædiat. **156**:124 (Jan.) 1941.

"(1) A method for the separation of cathepsin and pepsin in gastric juice is described.

"(2) The dependency of activity of cathepsin, isolated by this method, from p_H is described and illustrated by a curve.

"(3) The cathepsin of human gastric juice is not the same enzyme as renin. Clotting of milk at p_H 6-6.5, effected by human gastric juice, is to be attributed to the function of pepsin-parachymosin."

AUTHOR'S SUMMARY.

INVESTIGATIONS ON CONGENITAL STENOSIS OF THE PYLORUS: ITS TREATMENT AND PROGNOSIS, WITH REPORT OF 107 CASES RE-EXAMINED 1 TO 22 YEARS AFTER TREATMENT. R. RINVIK, Acta pædiat. **27**:296, 1940.

During the twenty year period between 1918 and 1938, 137 infants were treated for pyloric stenosis in the pediatric wards of the University Clinic of Oslo; 86 per cent were boys and 14 per cent girls; 5.8 per cent had been born prematurely. In 2 instances the lesion affected 1 of twins. In 54 per cent of the cases the patient was the first child born in the family, in 34 per cent the second and in

12 per cent the third; 2 infants were the eleventh children in their families. The median birth weight of the group was greater than the mean birth weight of Norwegian infants; the large majority were breast fed up to the time of appearance of symptoms. The average age at the onset of overt manifestations was 28.5 days; the onset was more frequently before this time than after it. The disease occurred more often in late spring than at other times of the year. Diagnosis depended on the usual points; the pylorus was palpated in 72 per cent of the cases. Since October 1934, roentgen confirmation has been sought in all cases; 50 patients have been so examined. The disease was recognized with increasing frequency during the latter part of the period covered by the survey.

As to treatment, 72 patients were handled conservatively and 65 were operated on. Irrespective of the type of therapy, the infants were all cared for in old fashioned wards, constructed in 1893 and unaltered since; they lack central heating and any provision for isolation. The use of small frequent feedings, preferably, but not always, of breast milk, was the mainstay of the conservative treatment. Gastric lavage, once popular, has been abandoned. Atropine sulfate in doses of 1.0 to 1.5 mg. (1/60 to 1/40 grain) thrice daily proved of little value. Atropine methyl nitrate (eumydrine) was found to be extremely effective. This substance, which is only about one-fiftieth as toxic as atropine sulfate, need be given in doses only 4 to 5 times as large as those required with atropine sulfate. The administration of 0.5 mg. (1/30 grain) of eumydrine in each of three to five feedings daily may be taken to be representative of current practice. Of the 72 patients treated conservatively, 6 died; if the figures are corrected by the exclusion of 4 cases in which the lethal outcome was clearly not due to defects inherent in the treatment, the mortality was 2.9 per cent. Two recurrences of short duration were observed. Sixty-five patients were operated on, some after medical treatment had failed to attain quick results. Five died, yielding a mortality of 7.6 per cent for the group in which operation was performed. Two complementary operations were required. At present, there is a tendency to treat more patients conservatively; this is due in large measure to the encouraging results obtained with atropine methyl nitrate.

A follow-up examination was made of 107 of the patients; the shortest interval since treatment was one year. In general, all the patients were well. Certain details of the follow-up inquiry are communicated. McCune, New York.

Nervous Diseases

Sulfapyridine Therapy in Pneumococcic Meningitis Complicated by Pulmonary Tuberculosis with Recovery. Suzanne Schaefer, New Orleans M. & S. J. **93**:83 (Aug.) 1940.

The author reports a recovery from type XIX pneumococcic meningitis which occurred during the course of treatment for an active tuberculous infection of both lungs (adult type) and tuberculous synovitis of the right knee.

The blood culture was positive for the same organism (type XIX).

The spinal fluid revealed a type XIX pneumococcic meningitis. A complication was left otitis. This was followed by mastoiditis and an extradural abscess above the knee of the lateral sinus.

The treatment consisted of administration of sulfanilamide, azosulfamide, sulfapyridine, type-specific rabbit serum and transfusions.

Recovery occurred with no exacerbation of the tuberculous processes.

Berkley, Los Angeles.

Influence of Pregnancy and Lactation on Susceptibility to Arrest of Brain Circulation. Herman Kabat, Proc. Soc. Exper. Biol. & Med. **44**:23 (May) 1940.

Previous studies (this journal, **38**:864, 1938; **42**:534, 1939) showed that puppies were much more resistant to complete arrest of the circulation in the brain

than were adult animals. This work revealed that both the pregnant and the lactating animal were more severely affected by brain stasis than was the normal adult dog.

HANSEN, Minneapolis.

THE IMMEDIATE TREATMENT OF CONVULSIONS IN CHILDREN. M. G. PETERMAN, Wisconsin M. J. **39**:375 (May) 1940.

First, protect the child from injury.

Second, if there is fever give an enema, a cold pack or a sponge bath to lower it. A hot pack may be dangerous (burns). A cleansing enema is followed by administration of a 50 per cent magnesium sulfate solution for retention.

If a sterile solution is available and needed, a 20 to 50 per cent solution may be given intramuscularly, or a 20 per cent solution may be given slowly intravenously.

If the convulsion persists, anesthetization with chloroform or vinyl ether is the most practical procedure. Status convulsivus will be fatal unless it is promptly treated.

In cases of tetanus the antitoxin should be given promptly, as well as tribromethanol by rectum.

For the convulsions of spasmophilia calcium is used. The chloride in 10 per cent aqueous solution may be given by mouth, 45 to 60 grains (2.9 to 3.8 Gm.), or by gavage if necessary, followed with 15 grains (0.97 Gm.) every six hours for two or more weeks. Viosterol in oil and acid milk are given coincidentally and continued for long periods.

Blood for examination should be taken before treatment is instituted whenever possible, and sugar, calcium and phosphorus determinations made. The author has never seen a true convulsion due to hypoglycemia.

Spinal puncture as a diagnostic and therapeutic aid should be done unless tumor of the brain is suspected.

In cases of intracranial hemorrhage in the newborn infant, blood found in the subarachnoid space should be drawn off rather than allowed to remain and either clot or absorb.

Opium should not be given in any form for convulsions.

JANNEY, Wauwatosa, Wis.

Psychology and Psychiatry

A STUDY OF THE RELATIONSHIP BETWEEN PSYCHOMETRIC PATTERNS AND PERSONALITY TYPES. MARJORIE GERLACH, Child Development **10**:269 (Dec.) 1939.

This study is concerned with the problem of the relation between the psychometric pattern as indicated by the Stanford Binet and the Cornell-Coxe quotient, and two broad personality types, namely, asocial and aggressive, as found in the case histories of a group of 61 white boys aged 9 through 12, referred to a clinic as classroom problems.

The relation between parental nativity, psychometric pattern and personality type is also considered, and, in turn, chronologic age is examined in regard to these three factors. Nine variations of the psychometric pattern are shown; three subgroups according to parental nativity are made.

Of the 61 subjects, 37 fall into the asocial group and 24 into the aggressive. It is then found that almost half the aggressive group has a psychometric pattern in which, on the level of average intelligence, the performance quotient is significantly higher than the verbal, while the pattern of only 13 per cent of the asocial group occurs here. The heaviest concentration of the asocial group is 30 per cent, at the level of below average intelligence, without significant difference between the performance and the verbal quotient.

By the rank-difference method coefficients of correlation are found for the Cornell-Coxe and the Stanford Binet rating of the two personality types, which

point toward a greater disparity between performance and verbal quotients for the aggressive group than for the asocial. The same is true within the groups according to parental nativity with the exception of that in which both parents are American born.

When chronologic age is concerned, the asocial group tends to cluster at 10 years, whereas the aggressive group, although more evenly distributed, averages somewhat higher.

GERLACH, New York.

AN ANALYSIS OF THE VARIANCE OF CONFLICT BEHAVIOR IN PRESCHOOL CHILDREN. MERRILL ROFF and LOUISE ROFF, Child Development **11**:43 (March) 1940.

Conflict behavior in two WPA nursery schools, one in Bloomington, Ind., and one in Chicago, was studied by the observational procedure used by Jersild and Markey, and the results were compared with their results for three New York groups. The average number of conflicts in each group was found to be below their general average.

An analysis of the variance of conflict frequency in one group for which complete records were obtained and in the three nursery school groups studied by Jersild and Markey was made. This analysis indicated that about one-half the conflict variance was attributable to causal factors which differ from group to group but that no single general factor, such as economic status, was significantly related to conflict frequency, when all the groups were considered. Also, no significant relation was found between the number of conflicts and age, sex or intelligence. Differences in nursery school conditions, such as the number of teachers, frequency of "teacher interference" and amount of play space and equipment, did not, within the limits of variation of these groups, seem influential. Consideration of these results indicates the necessity for a more concrete and specific description of the non-nursery-school settings of the different groups of children, with particular emphasis on their family situations. A clear picture of the conditioning factors will require, among other things, a more adequate description of adult behavior from the point of view of its effect on children than is now available.

FROM THE AUTHORS' SUMMARY.

HOW CHILDHOOD FEARS TOWARD DENTISTRY CAN BE CONTROLLED. GEORGE E. MORGAN, J. Am. Dent. A. **27**:766 (May) 1940.

The problem of controlling child behavior in the dental office differs from the problems of child psychology in the home or school. Childhood fears toward dentistry are acquired and influenced for good or bad by the attitude of the parents or teacher and the attitude of the dentist. Most children are placid and accept dental care as they do other things in life, with a matter-of-fact attitude.

However, three types of personality patterns present a problem of management from the standpoint of dentistry:

1. The timid type who demonstrates no initiative.
2. The bullying or obstinate type, active, a bluffer, apparently brave.
3. The shy or bashful child who suffers from lack of courage.

PREWITT, Lexington. [Angle Orthodontist]

PSYCHIATRY IN THE SERVICE OF THE SCHOOLS. HENRY C. SCHUMACHER, J. Michigan M. Soc. **39**:307 (May) 1940.

The author outlines the role that psychiatry may play in the development of the "total child."

He points out that the disturbance in behavior and conduct has an incipient stage and shows the need of attention during this stage. The role of defects as a contributing factor to maladjustment is discussed.

Psychiatry has made its contribution by calling attention to the physical and mental (emotional) symptoms which are common indicators of a maladjusted state.

In many centers it also has provided facilities for treatment of these conditions.

GRASPING AND SUCKING. IRVING BIEBER, J. Nerv. & Ment. Dis. **91**:31 (Jan.) 1940.

The relationship between the grasping and sucking reflexes in the newly born and in young infants is discussed. In older children and adults these functions are present only in pathologic states. The case of a 48 year old man in whom sucking and grasping reflexes returned is cited. The man suffered from hypertensive cerebrovascular disease and multiple cerebral softening.

JAHR, Omaha.

THREE CASES OF GENUINE AND ONE CASE OF CEREBRAL PUBERTAS PRAECOX. E. SIGRIST, Ann. pædiat. **155**:84 (May) 1940.

A girl of 7 years, a boy of 6½ years and the boy's brother of 8 years showed the characteristic signs of puberty: accelerated increase of body length and weight, growth of genital organs to maturity and development of secondary sexual characteristics. The blood picture, ossification and dentition showed the development of normal maturity. Only the psyche corresponded to the age. There was marked hyperglycemia, both during fasting and after ingestion of sugar. At 10 years these precocious children had completed their somatic development and were grown up. The psyche of each was still infantile.

Thus there are presented 3 cases of genuine pubertas praecox. The occurrence of the condition in 2 brothers (cases 2 and 3) and the mental and physical male traits of the mother of the patient in case 1 make it probable that hereditary factors are involved.

Following Schmëing's theory of the stages of maturation it could be an atavism, a regression to the state of primitive man who attains sexual maturity in the infantile stage of civilized man. A boy of 3 years exhibited well developed secondary sexual characteristics with advanced body length but small testicles. At the same time he had an oxycephalic skull and slight hydrocephalus and was imbecile. His case should be considered one of pseudo pubertas praecox cerebralis.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Genitourinary Tract

PYELITIS. T. H. OLIVER, Practitioner **145**:1 (July) 1940.

The ketogenic diet was introduced after the discovery that betahydroxybutyric acid was lethal to Bacillus coli. It was most successful, but its unpleasantness has made it now of only historical interest, and it has been replaced by mandelic acid or one of its compounds. If mandelic acid itself is used, it is essential that the urine should be acidified to p_H 5.5 by giving ammonium chloride at the same time. As many patients are nauseated by ammonium chloride, ammonium mandelate is now generally used.

This treatment is effective, not only for B. coli, but for Streptococcus faecalis and to a lesser extent for Bacillus proteus. A frequent practical difficulty is to reach the required acidity of the urine and to insure a sufficient concentration of the drug. Nausea may prove troublesome in treatment, and occasionally there may be definite symptoms of toxemia with severe urticarial rashes.

Recently the sulfonamide group of drugs has tended to replace mandelic acid. They are quite as powerful in their effect on B. coli and in addition are more active against Str. haemolyticus and B. proteus. They have also the advantage that they are more active when the urine is alkaline and so can be given in conjunction with potassium citrate.

Toxic symptoms, apart from some cyanosis, are rarely severe, although in a few instances prostration or vomiting may compel discontinuance of the treatment and the substitution of mandelic acid. GELSTON, San Francisco.

INTRAMUSCULAR INJECTION OF UROSELECTAN FOR PYELOGRAMS IN INFANTS. VINCENT VERMOOTEN, South African M. J. **14**:339 (Sept. 14) 1940.

Satisfactory urograms were obtained after the intramuscular injection of uroselectan B (neo-iopax) into 2 infants 5 months old. TENNEY, Madison, Wis.

USE OF SULFANILAMIDE AND ITS DERIVATIVES IN CERTAIN URINARY INFECTIONS. P. LEREBOULLET, Paris méd. **2**:264 (Nov. 4) 1939.

The author reports favorable results in infants and children. One case of severe pyelitis caused by the colon bacillus, with blockage of the ureter and swelling of the kidney, responded rapidly to sulfapyridine (2-[paraaminobenzene-sulfonamido]-pyridine). LESLIE, Evanston, Ill.

TREATMENT OF HEMORRHAGIC GLOMERULONEPHRITIS WITH ASCORBIC ACID. L. ANGELINI, Pediatria **47**:762 (Sept.) 1939.

The author treated 14 patients with acute hemorrhagic glomerulonephritis and 1 case of the subacute condition with ascorbic acid given intravenously. A dose of 0.1 grain (6 mg.) was given once daily for fifteen to twenty-five days. After the third or fourth injection there were noted clearing of the urine (disappearance of the macroscopic hematuria) and an increase of diuresis. The general condition was improved, and in edematous patients there was a disappearance of the edema. Microscopic examination showed red blood cells to be still present for two to four weeks after the disappearance of gross hematuria. The author concludes that ascorbic acid is useful in the treatment of hemorrhagic nephritis.

MARTOCCIO, Utica, N. Y.

CYSTOGRAPHY IN INFANCY. AGUSTIN CASTELLANOS and RAÚL PEREIRAS, Arch. de med. inf., Habana **9**:160 (July-Sept.) 1940.

By use of a 50 per cent neosilvol solution the authors believe that a preliminary exploration should be done in all cases of pyelitis before pyelograms are taken. This method is antiseptic and safe. It will show any anatomic defects of the bladder and urinary tract. SANFORD, Chicago.

Diseases of the Ductless Glands; Endocrinology

A REVIEW OF EXPERIMENTAL AND CLINICAL TRIALS OF STILBESTROL. DOROTHY W. ATKINSON, Endocrinology **27**:161 (Aug.) 1940.

After reviewing and correlating the various published papers concerning stilbestrol, the author concludes that the value of the synthetic estrogens as compared with the natural estrogens lies in their lower cost and their high oral potency. If the toxic side effects can be reduced or eliminated by further chemical refinements, it seems probable that use of the natural estrogens will be eliminated in clinical practice or that their cost will be reduced. JACOBSEN, Buffalo.

THE EFFECT OF THE ANTERIOR PITUITARY-LIKE SEX HORMONE [CHORIONIC GONADOTROPIN] AND OF CASTRATION ON EXPERIMENTAL TUBERCULOSIS. C. BERNARD BRACK and LAMAN A. GRAY, Endocrinology **27**:322 (Aug.) 1940.

No difference in the severity of tuberculosis between a group of noncastrated female rabbits receiving chorionic gonadotropin (antuitrin-S) and a group of noncastrated control animals was demonstrated. The same experiment with castrated animals showed no difference in the two groups. JACOBSEN, Buffalo.

FEMINIZATION AND DEMASCULINIZATION OF A 17-YEAR-OLD GIRL BY INJECTIONS OF STILBESTROL. H. LISSER, Endocrinology **27**:385 (Sept.) 1940.

A girl aged 16 years with masculine characteristics was feminized by injections of stilbestrol.

JACOBSEN, Buffalo.

THE SPECIFIC METABOLIC PRINCIPLE OF THE PITUITARY. ROBERT N. FEINSTEIN and EDGAR S. GORDON, Endocrinology **27**:592 (Oct.) 1940.

Experiments on human beings and on rabbits in metabolism chambers indicated that the pituitary contains a metabolic stimulant which is not present in similarly prepared liver extracts.

JACOBSEN, Buffalo.

FURTHER PURIFICATION OF THE GROWTH HORMONE OF THE ANTERIOR PITUITARY. HEINZ L. FRAENKEL CONRAT, DONALD L. MEAMBER, MIRIAM E. SIMPSON and HERBERT M. EVANS, Endocrinology **27**:605 (Oct.) 1940.

Alkaline extraction of anterior pituitary glands and treatment of the extract with cysteine resulted in an increase in growth-promoting activity and a decrease in contamination with other hormones.

This indicates that the growth-promoting effects of pituitary extracts cannot be attributed to a synergistic action between these other hormones.

JACOBSEN, Buffalo.

ON THE QUESTION OF THE PRESENCE OF THYROGLOBULIN IN THE BLOOD. LAWRENCE I. STELLAR and HARRY G. OLKEN, Endocrinology **27**:614 (Oct.) 1940.

Under a variety of conditions a test for thyroglobulin sensitive up to 1 part in 150,000 gave no indication of the presence of this protein in human blood.

JACOBSEN, Buffalo.

THE EFFECT OF ADRENALIN IN PEANUT OIL AND ADRENALIN PELLETS UPON THE THYROID GLAND OF THE GUINEA PIG AND RABBIT. CARL GOETSCH, Endocrinology **27**:617 (Oct.) 1940.

Experiments are reported which indicate that epinephrine in peanut oil does not influence the thyroid glands of guinea pigs but when given to rabbits in adequate doses for long periods causes a change in the character of the mitochondria, which may be interpreted as representing stimulation.

JACOBSEN, Buffalo.

THE ENDOCRINE DYSCRASIA OF ACNE VULGARIS IN WOMEN. CHARLES H. LAWRENCE and NICHOLAS T. WERTHESSEN, Endocrinology **27**:755 (Nov.) 1940.

A significant decrease from the normal in urinary excretion of estrogen by women with acne was demonstrated. No significant change in excretion of urinary androgenic material was observed.

The following features are pointed out: the characteristic limitation of acne to the pubertal period; the frequent association of the eruption with abnormal menstruation, and the reports in the literature of the appearance of acne in female patients under treatment with testosterone, followed by its disappearance when the treatment was omitted. All this evidence is consistent with the thesis that a disturbance of the androgen-estrogen ratio is a significant etiologic factor in acne in women.

JACOBSEN, Buffalo.

BLOOD SUGAR STUDIES IN A CASE OF ADIPOSO-GENITAL DYSTROPHY SHOWING CHRONIC HYPOGLYCEMIA. JAMES FINLAY HART, Endocrinology **27**:759 (Nov.) 1940.

Extensive studies of the blood sugar levels under various experimental conditions were made. It is concluded that the values for blood sugar in the case studied were very stable and responded only to excessive doses of epinephrine and that there was a noticeable tendency on the part of the sugar metabolism to keep the blood sugar at subnormal levels, even to the extent of causing a spill of sugar into the urine at those levels.

JACOBSEN, Buffalo.

SIMMONDS' CACHEXIA. JOSEPH C. DOANE, NATHAN BLUMBERG and GEORGE TEPLICK, Endocrinology **27**:766 (Nov.) 1940.

In the treatment of more than 500 obese patients with amphetamine (benzedrine) sulfate the average loss of weight was 3.2 pounds (1.4 Kg.) per week for a course of treatment (three to twelve weeks).

The possibility of untoward reactions is pointed out, although in this series there were no serious ones.

JACOBSEN, Buffalo.

LIVER DAMAGE AND ESTROGEN INACTIVATION. GREGORY PINCUS and DOROTHY WEBSTER MARTIN, Endocrinology **27**:838 (Nov.) 1940.

Several investigations have demonstrated that the mouse liver and the rat liver inactivate estrogen in vitro.

From the experiments reported (on 105 ovariectomized rats) it is concluded that damage to the liver due to carbon tetrachloride does not reveal the presence of endogenous extraovarian estrogen in spayed animals but increases the effectiveness of administered estrogen, presumably by interfering with detoxification.

JACOBSEN, Buffalo.

ON THE PROTECTIVE ACTION OF TESTOSTERONE AGAINST THE KIDNEY DAMAGING EFFECT OF SUBLIMATE. HANS SELYE, J. Pharmacol. & Exper. Therap. **68**:454 (April) 1940.

In previous work the author has noted that in the mouse testosterone caused an increase in the size of the kidney, due mainly to hypertrophy of the cells of the proximal and distal convoluted tubules. He has also shown that even under normal conditions the kidney is probably under the controlling influence of the testis. It was stated, furthermore, that testosterone in sufficiently high doses restores the atrophic kidney of the castrate male to normal. In view of these and other facts, female mice were given testosterone until the physiologic effect was obtained and then, with an equal number of controls, corrosive sublimate solution subcutaneously to the point of toxicity. Of the control mice seven died before the fifth day when the other three were killed; of the group treated with testosterone none had died on the fifth day, when all were killed for histologic study. The group treated with testosterone showed the aforementioned renal hypertrophy, and the marked degeneration of tubular epithelium observed in the controls was almost absent in the group treated with testosterone. The author raises the question of a possible similar beneficial effect of androgens in case of tubular damage in man.

PILCHER, Cleveland.

EFFICACY OF PELLETS OF POSTERIOR HYPOPHYSIS AND OF PITRESSIN IN OIL IN DIABETES INSIPIDUS. J. A. GREENE and L. E. JANUARY, Proc. Soc. Exper. Biol. & Med. **44**:217 (May) 1940.

Attempts to implant pellets of dried posterior pituitary gland were unsuccessful both in 4 cats with experimentally produced diabetes insipidus and in 2 patients with diabetes insipidus. Pitressin tannate in oil, 1 cc., ameliorated the manifesta-

tions in 3 cats for three to seven days and in 3 men for thirty to eighty-two hours. The symptoms were controlled in the 3 human subjects by a subcutaneous injection of 1 cc. every thirty-six to fifty-seven hours. No unpleasant or deleterious local or general reactions occurred.

HANSEN, Minneapolis.

ZINC SALTS AND OIL IN PROLONGATION OF THERAPEUTIC EFFECT OF PITRESSIN IN EXPERIMENTAL DIABETES INSIPIDUS. D. J. STEPHENS, Proc. Soc. Exper. Biol. & Med. **44**:240 (May) 1940.

In a study of a dog with experimental diabetes mellitus it was found that the presence of 0.1 per cent zinc acetate prolonged and intensified the action of aqueous solution of pitressin. Pitressin in oil, on the other hand, exerted a much more prolonged and intensified effect.

HANSEN, Minneapolis.

THE THYREOTROPHIC HORMONE AND ITS RELATION TO CLINICAL SYNDROMES. C. G. LAMBIE, M. J. Australia **2**:819 (Dec. 2); 853 (Dec. 9) 1939.

Part I of this article is an excellent review of the present knowledge of the physicochemical properties and physiologic action of the thyrotrophic hormone of the pituitary gland. Part 2 discusses the relation of the thyrotrophic hormone to clinical syndromes.

This paper does not lend itself readily to abstracting, but should be read by every one interested in endocrinology.

GONCE, Madison, Wis.

ABSORPTION OF FAT AND HYPOPHYSIAL SECRETION. DOMENICA BORI, Riv. di clin. pediat. **38**:170 (March) 1940.

Puppies were fed a measured diet of bread and milk. The fat content of the food and of the feces was carefully determined. The normal absorption of fat was 98 per cent; after the animals were given extract of posterior pituitary intravenously, the absorption fell to 94 per cent. Similar injections of extract of anterior pituitary resulted in increasing the absorption of fat from 98 per cent to 99.5 per cent. Thus the anterior pituitary product increased the absoption of fat, while the posterior pituitary product decreased its absorption. An antagonistic action appears to exist between the two parts of the hypophysis in regard to the absorption of fat.

HIGGINS, Boston.

DIABETES INSIPIDUS. J. D. LEBRET, Maandschr. v. kindergeneesk. **9**:200 (Feb.) 1940.

The author presents a description of a boy 6 years old who has been treated and greatly improved by the principle of the posterior part of the hypophysis administered as snuff powder. The use of this powder should be continued. A review of the literature on diabetes insipidus is included.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Muscles, Bones, Joints and Lymph Glands

THE SKELETAL AND DENTAL PATHOLOGY OF AN EARLY IRANIAN SITE. WILTON MARIAN KROGMAN, Bull. Hist. Med. **8**:28 (Jan.) 1940.

This article contains much material on pediatric paleopathology for the period about 4000 B. C. to about 2000 B. C. The condition of the children's teeth was "uniformly good"; only 3 cases of caries and 2 of apical abscess were found. One child showed traumatic loss of the upper central incisors. There was excessive wear of the teeth; at 7 to 8 years of age—just prior to the eruption of the premolars—the temporary molars showed "complete loss of enamel from the occlusal surface" (fourth degree of wear), probably due to gritty food. There was no

crowding or malposition. The eruption pattern of permanent teeth and the form of the palatal arch "give some evidence of retention of primitive features."

A careful description of a microcephalic cranium (Hissar III, about 3000 B. C. to about 2000 B. C.) of a child of about 6 years is given; there were complete obliteration of the sagittal suture, microcephalic measurements and asymmetry of the vault in form as well as in thickness, simulating to a certain extent hemiatrophy.

Three unilaterally shortened humeri may present a "hereditary familial condition," though the ulnas and radiuses on the affected side show no atrophy from disuse. The symmetry of the length relations indicates a congenital condition.

ROSENTHAL, St. Paul.

GIANT CELL TUMOR OF THE FRONTAL BONE. J. J. KEEGAN and CHARLES P. BAKER, J. Lab. & Clin. Med. **26**:319 (Nov.) 1940.

A case of benign giant cell tumor in a 13 year old boy is reported because of the unusual location of the growth, only 1 other such case having been reported previously.

GARD, Galveston, Texas.

EARLY DIAGNOSIS AND TREATMENT OF OSTEOMYELITIS IN THE CHILD. ALFREDO RODRIGUEZ CASTRO, Bol. Inst. internac. am. de protec. a la infancia **13**:317 (Oct.) 1939.

1. The treatment of hematogenous osteomyelitis can by no means be uniform; in view of the extraordinary clinical polymorphism of the disease, the therapeutic proceeding must be variable and adapt itself to the characteristics of every single case.

2. From a practical point of view, it is important to distinguish between staphylococcic septicemias and serious osteomyelitis with a more or less transitory bacterial state. The former, always extremely grave, should be treated at first exclusively by medical means.

3. For acute osteomyelitis, frankly localized, the author advocates the expectant treatment recommended by Leveuf and Debré in France: immobilization in plaster duly applied and adequate auxiliary treatment (transfusions, vaccination, anatoxin, etc.). The general phenomena being appeased and the local process becoming sufficiently developed (from nine to ten days generally), the surgical treatment comes in.

4. In chronic diseases thorough cleansing and regularization of the focus will be necessary, in order to eliminate sequestrums and to remove, as much as possible, residual hard-walled cavities.

FROM EDITOR'S SUMMARY.

ACUTE OSTEOMYELITIS IN THE CHILD. CARLOS URRUTIA URRUTIA, Bol. Inst. internac. am. de protec. a la infancia **13**:732 (April) 1940.

1. In Chile acute hematogenous osteomyelitis is a common disease, as is indicated by 70 cases observed during seven years in the surgical service of a hospital in Santiago having a capacity of 84 patients.

2. The morbidity rate was 0.82 per cent and the mortality rate 8.75 per cent.

3. Diagnosis of this condition should be made clinically, for positive roentgen evidence may be obtained only after ten days.

4. Up to the present the treatment has been primarily surgical. Transfusions and sulfanilamide are used in some cases.

5. In the surgical treatment, first subperiosteal incisions are made and afterward extensive canalizations are done; only exceptionally is trephining or diaphysectomy necessary.

6. In the operative wounds only gauze drains are left, and in the canalizations sterile petrolatum and an immobilizing plaster apparatus are applied. Dressing of the wounds should be done as seldom as possible.

7. Local chemical products, whether antiseptic or caustic, are more dangerous than profitable; the biologic ones give no advantages.

8. The hospital organization, with a polyclinic annexed to the service, reduces the time that the patients stay in the hospital; this is economically advantageous.

FROM EDITOR'S SUMMARY.

PRIMARY CAVERNOUS HEMANGIOMA OF SKULL. GUSTAV SOMMER, Beitr. z. klin. Chir. **168**:101, 1938.

A case is reported of a large cavernous hemangioma in the occipital region in a 16 year old girl. This was removed operatively, with a favorable result.

RUBIN, Boston.

THE TREATMENT OF CONGENITAL DISLOCATION OF THE KNEE. BEDŘICH FREJKA, Bratisl. lekár. listy **17**:466 (Oct.) 1937.

The cause of the dislocation may be faulty uterine position with degeneration of the quadriceps tendon, often complicated by patellar aplasia and shortening of the muscles of extension. At times spontaneous cure takes place, but secondary fracture may result. Surgical correction consists of gradual plastic elongation of the patellar ligaments or plastic elongation by distribution of the quadriceps tendon and of the patellar ligaments. In cases in which congenital dislocation of the hip is present as a complication the defect of the hip is treated first.

STULIK, Chicago.

DYSTROPHIA MUSCULORUM PROGRESSIVA IN SIX BROTHERS. T. H. VAN LOON-WIERINGA, Maandschr. v. kindergeneesk. **9**:333 (May) 1940.

This paper is a description of 6 brothers ranging in age from 7 to 16 years, all suffering from dystrophia musculorum progressiva. Changes in the creatine-creatinine metabolism are discussed. Administration of aminoacetic acid during two years gave some amelioration in the less severe conditions and no progression of the more advanced forms.

VAN CREVELD, Amsterdam, Netherlands.

PROGRESSIVE MYOSITIS OSSIFICANS. S. VAN CREVELD and J. M. SOETERS, Maandschr. v. kindergeneesk. **9**:427 (Aug.) 1940.

The results of an extensive clinical and roentgen examination of a girl suffering from progressive myositis ossificans are communicated. A biopsy was performed at two different stages of the disease, and the results of histologic and microchemical investigation are given. The metabolism was studied in order to get an insight into the pathologic physiology of the disease. Different therapeutic measures, partly based on recent studies, were tried, with disappointing results. The outcome of treatment with parathyroid extract was remarkable in that the calcium content of the serum, after a number of injections of the substance, no longer showed any important increase.

VAN CREVELD, Amsterdam, Netherlands.

Skin Diseases; Allergy

PARENTERAL USE OF HYPERTONIC DEXTROSE FOR RELIEF OF PRURITUS AND OF SERUM SICKNESS. O. MILTON STOUT and ROBERT J. KOSITCHEK, Arch. Dermat. & Syph. **42**:802 (Nov.) 1940.

Observations on the therapeutic effect of hypertonic solution of dextrose on patients with serum sickness and certain types of pruritus are presented.

The series comprised 58 patients who presented pruritus as an outstanding symptom. The most noteworthy results were obtained in 10 patients with serum sickness. Three of them had failed to respond to intensive treatment with epinephrine hydrochloride and calcium gluconate. In the 10 patients the results were immediate, consistent and complete, not only in relief of pruritus but in relief of the accompanying articular pains, urticaria and fever.

JACKSON, Iowa City.

EXPERIMENTAL AND CLINICAL OBSERVATIONS WITH HISTAMINASE. ALFRED F. KNOLL and LAWRENCE G. BEINHAUER, Arch. Dermat. & Syph. **42**:896 (Nov.) 1940.

The authors' studies led to the following conclusions:

The syndrome of anaphylaxis in guinea pigs is unaffected by pretreatment with histaminase.

Intracutaneous wheals produced by histamine in normal as well as in allergic persons are not altered by oral pretreatment with histaminase.

Of 101 patients suffering from diseases on an allergic basis and 33 patients suffering from miscellaneous disturbances treated with histaminase, pronounced improvement was obtained in only 35, or 26.1 per cent. The unimproved group was treated for six weeks with an average daily dose of 50 units. More than one-half the patients who were decidedly improved were afflicted with atopic dermatitis or acute urticaria, two diseases given to spontaneous regression and even complete involution. Interpretation of the improvement noted in these cases is therefore difficult.

The results with acne vulgaris were practically negative.

The toxic effects from histaminase were negligible. JACKSON, Iowa City.

INTRINSIC ASTHMA. FRANCIS S. RACKEMANN, J. Allergy **11**:147 (Jan.) 1940.

This is a thought-provoking article describing a group of 283 patients whose asthma bore no relation to changes in season, environment or diet.

The mortality rate in this "intrinsic" group was 8 per cent, whereas in a group of 2,000 cases in which an extrinsic factor was the cause of the condition, the mortality rate was nil except for an occasional death that could be attributed to some accident, such as too large a dose of desensitizing substance to a very sensitive patient.

The "intrinsic" group is made up chiefly of adults, especially those in middle age.

"The theories concerning the nature of intrinsic asthma are discussed, with the suggestion that allergy is only one of the exciting causes of a group of symptoms which together make a syndrome characterized by asthma, by lesions in the nasal and sinus membranes and by eosinophilia, as well as by the less definite 'allergic toxemia.' Behind the syndrome must be some fundamental disturbance—an "x" factor—so far entirely unknown, but which may occur in excess rather than in deficiency. Even if it can be proved to be a histamine-like substance, the reason for its abnormal occurrence remains to be determined." HOYER, Cincinnati.

Surgery and Orthopedics

SOME COMMENTS ON THE TREATMENT OF CONGENITAL CLUBFEET. J. H. KITE, J. M. A. Georgia **29**:212 (April) 1940.

This is a plea for the early conservative (nonoperative) treatment of congenital clubfoot. It is well to remember that Dr. Kite, Michael Hoke and Lawson Thornton first described the conservative nonoperative treatment with plaster casts

and wedgings, which may be performed without an anesthetic, the use of force or any cutting operations.

It is generally conceded among orthopedists of the present era that this is the treatment of choice. This method takes longer than the radical operative treatment, but better results are obtained, the normal appearance of the feet is restored and, because there is usually freedom from adhesions, normal function results.

The details of the cast and wedging method are described in detail and fully illustrated in the June 1939 issue of the *Journal of Bone and Joint Surgery.*

MORRISON, Savannah, Ga.

HYPERTONIC SODIUM SULPHATE TREATMENT OF INFECTED WOUNDS. J. C. LYTH, Lancet **1**:216 (Feb. 3) 1940.

In the past four years the author has treated all infected wounds, i. e., all wounds not operative, a total of 1,096, with hypertonic sodium sulfate solution in the form of soaked compresses applied to the surface. No bactericidal antiseptic was used. The results were astonishingly good. Lyth attributes the good results to the fact that the osmotic pressure of the hypertonic solution is exerted not at the point of application but at the cell walls in the tissues and lymphatic capillaries, often at a considerable distance from the point of application. The solution is not bactericidal, but since cellular edema is apparently a requisite for the metabolic processes of bacteria, it may be that a reversal of this edema interferes with these processes.

LANGMANN, New York.

FRACTURES OF THE ELBOW IN CHILDREN. PADRO SANCHEZ TOLEDO, Cir. ortop. y traumatol., Habana **6**:14 (Jan.-March) 1938.

In the course of two years 297 fractures of the elbow were treated at the Municipal Hospital for Children. These may be classified, according to their order of frequency, as follows:

Supracondylar fracture	197
Epitrochlear fracture	32
Fractures of the neck of the radius	30
Fracture of the external condyle	20
Fracture of the olecranon	7
Monteggia's fracture	5
Supracondylar and epitrochlear fracture	2
Epitrochlear and epicondylar fracture	1
Fracture of the olecranon and head of the radius	2
Fracture of the olecranon and epitrochlea	1

In 20 cases of fracture of the external condyle the fragment was sutured with kangaroo tendon, and malunion occurred in only 2 cases.

Among the 32 epitrochlear fractures, there were 8 in which a severe displacement could not be corrected. Seven were fixed with kangaroo tendon and 1 with a nail. In almost all of them there appeared slight secondary displacement.

Monteggia's fracture, which occurred in 5 cases and which they generally include among fractures of the elbow, was treated as follows: In compound fractures they sutured the ulna and performed manual reduction of the head of the radius. In 4 cases they obtained an excellent reduction by the help of an apparatus of Inclan's invention for the reduction of fractures of the forearm.

About one half of the 197 supracondylar fractures did not present any displacement.

In all cases, observed by them after intervention for supracondylar fracture there has developed almost complete ankylosis of the elbow (4 cases).

All fractures of the olecranon lacked displacement, except 1 in which there developed pseudarthritis. This healed perfectly, however, after freshening and osteosynthesis.

For fractures of the radial neck with angulation or great displacement surgical intervention became necessary, and frequently a tendency to new bone formation with secondary block of the joint was noticed. The prevalent type was the penetrating fracture without displacement.

HERRON, Oak Ridge, La.

PLASTIC TENDON OPERATION REPAIR FOR LOSS OF OPPOSITION OF THE THUMB FOLLOWING INFANTILE PARALYSIS. ALBERTO INCLAN Y RAUL RODRIGUEZ, Cir. ortop. y traumatol., Habana **6**:140 (July-Sept.) 1938.

Following the technic of Bunnell in his work reported in the *Journal of Bone and Joint Surgery* for April 1938, the authors have used this technic and obtained good results in 1 case of infantile paralysis in which the patient could not oppose the thumb toward the palm of the hand.

HERRON, Oak Ridge, La.

REGARDING THE QUESTION OF NECESSITY OF TREATING UMBILICAL HERNIA AND PHIMOSIS IN INFANCY. I. SCHARFF, Med. Klin. **35**:1571 (Dec. 8) 1939.

Scharff advocates no treatment for umbilical hernia unless the lesion is large and greatly protruding. He states that he and his associates have observed even rather large hernias which closed spontaneously after two or three years.

Phimosis during the first year is physiologic and requires treatment in few instances.

SIEMSEN, Chicago.

Teeth and Dentistry

THE EFFECT OF CITRUS FRUIT JUICES AND OF VARIOUS MOUTH PROPHYLAXES ON THE ORAL FLORA. H. J. FLORESTANO, J. E. FABER and L. H. JAMES, J. Bact. **39**:24 (Jan.) 1940.

This is a most interesting presentation. Quantitative determinations of the micro-organisms found in the saliva of 9 normal persons were made by the authors before and after each patient had used the following materials: water, orange juice, grapefruit juice, hexylresorcinol tooth paste and mouth wash, sodium ricinoleate tooth paste and mouth wash and a liquid dentifrice. "Plain agar was used for enumerating saprophytic types, tomato juice agar for aciduric organisms, and blood agar for potential pathogens. Samples of saliva were examined before lunch, after lunch, after prophylaxis and 2 hours later."

Using the "after lunch" counts as a 100 per cent basis for determining the average percentage decrease in bacterial counts immediately after prophylaxis, the investigators found that the counts for sodium ricinoleate tooth paste and mouth wash and for liquid dentifrice were, respectively, 89 per cent and 86 per cent less than the counts obtained after lunch. With hexylresorcinol tooth paste and mouth wash, the decrease was 59 per cent; with grapefruit juice, 56 per cent, and with orange juice, 47 per cent.

Although sodium ricinoleate tooth paste and mouth wash and liquid dentifrice were most effective in the actual removal of organisms, they were least effective in inhibiting further microbial action. "When the counts immediately after prophylaxis were used as a 100 per cent basis for determining the average percentage increase two hours later, the citrus juices were found to be the most effective in checking microbial activity."

STOESSER, Minneapolis.

Miscellaneous

ADOLESCENCE. BERT I. BEVERLY, J. Michigan M. Soc. **39**:23 (Jan.) 1940.

This article was read at the annual meeting of the Michigan State Medical Society, Grand Rapids, Mich., Sept. 19, 1939.

While perhaps little is presented that is new or startling for the pediatrician, there is much stimulation for general practitioners, especially for those removed from medical centers and child guidance clinics.

Following the technic of most mental hygienists, the author gives bits of personal histories of patients.

The summary concluding the article will probably find general acceptance by most of his readers.

CAREY, Detroit.

EFFECTS UPON MONKEYS OF SULFAPYRIDINE IN DOSES COMPARABLE WITH THOSE USED FOR INFANTS. JOHN A. TOOMEY, HERBERT S. REICHLE and WILLIAM S. TAKACS, J. Pediat. **16**:179 (Feb.) 1940.

A series of experiments was performed on monkeys (Macacus malatta). Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was administered in a dose less than that usually recommended for infants and young children but comparatively greater than that recommended for older children and adults. Many of these monkeys showed a decrease in the total number of red blood cells and in the hemoglobin content of the blood. In addition, an increase in the total number of white cells, an occasional reversal of the leukocyte-lymphocyte ratio and an increase in the urea content of the blood were noted. Toxic reactions seen in these animals were due in part to the formation of concretions in the straight tubules of the kidney, the renal pelves, the ureters or the bladder, with obstruction to the urinary flow; in part to consequent infections of the urinary tract, and in part probably to an immediate toxic effect of the drug on the epithelium of the convoluted tubules. In a few experiments sodium sulfapyridine was found to be more toxic than sulfapyridine when it was used in doses comparable to those recommended for sulfapyridine. Large amounts of fluid did not prevent the formation of stones. Two of the animals given ammonium chloride with the sulfapyridine had no lesions of the urinary tract.

RAUH, Cincinnati.

THE ACTION OF SULFAPYRIDINE (2-SULFANILYL AMINOPYRIDINE). H. M. POWELL and K. K. CHEN, J. Pharmacol. & Exper. Therap. **67**:79 (Dec.) 1939.

Some of the most recently discovered therapeutic agents have been used in man without a full and careful study of their effects in animals. Among them is sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), and fortunately its life-saving actions have far outweighed its rare deleterious or even possibly fatal actions. However, a study of the effects of the drug in animals is of course most valuable, and the actions seem in general to parallel those observed in man. In this study sulfapyridine was more effective against Pneumococcus and against Staphylococcus aureus than was sulfanilamide; it was equally effective against streptococci and meningococci and less effective in cases of typhoid infection. Neither drug was effective in mice poisoned with rabies or influenza virus. Among the characteristics of sulfapyridine are its low absorbability by mouth and its lack of action by vein in dilute solution on respiration and circulation. It is much less readily excreted in urine by animals than by man. Owing to its difficult absorption, daily oral administration of large doses of sulfapyridine to dogs does not produce significant changes in body weight, erythrocytes, leukocytes, hemoglobin, blood p_H or plasma carbon dioxide content, nor are there any pathologic lesions which can be attributed to the drug. (In man and in monkeys it is known to form renal calculi.)

PILCHER, Cleveland.

Book Reviews

Born That Way. By Earl R. Carlson, M.D. Price, $1.75. Pp. 174, with no illustrations. New York: The John Day Company, Inc., 1941.

This is a unique book, written by a man with spastic paralysis. Naturally, the author understands intimately the physical and emotional problems, the hardships and the practical difficulties which impede the course of the person with spastic paralysis.

Though seriously handicapped, Dr. Carlson by his own will power has successfully completed a medical education and found an important place in the world; he devotes himself to helping others solve the problems he faced. It is rare indeed for an author to possess such unusual qualifications for writing an interesting autobiography. His own story carries a message of hope and understanding and reflects a zeal to succeed which could hardly be matched. To the person with spastic paralysis he brings new ideas and encouragement, for every page is filled with practical suggestions.

The book is intended for the lay reader and will inspire thoughtful consideration by any handicapped person; in it the mothers and teachers of such persons will find the answers to many of their questions. To the workers who in one way or another deal with crippled children, those with spastic paralysis, by their number alone and perhaps because of the seeming hopelessness of the condition, have presented especially trying problems. To such workers "Born That Way" will be particularly welcome and should help to prove the author's contention that no matter how badly handicapped one may be there is a place in the world for every one.

Photodynamic Action and Diseases Caused by Light. By Harold Francis Blum, Ph.D. Price, $6.00. Pp. 309, with 50 illustrations and 25 tables. New York: Reinhold Publishing Corporation, 1941.

This book should prove of interest, although perhaps not of great practical value, to any member of the medical profession. The first chapters discuss the quantum theory of light and its application to biologic phenomena which occur under the influence of light rays, including those beyond the visible range. The distinction between the mode of action of ultraviolet light and that of light of the longer wavelengths is of interest, since the former acts directly on living tissue and the latter requires the mediation of some such substance as a photosensitive dye and oxygen. Examples of the latter mode of action are found in diseases of sheep, hypericum (St.-John's-wort) poisoning and *Geldekopf*. The situation with regard to human diseases is not so clear. On the basis of the evidence presented, the author questions that hematoporphyrin plays a role as a sensitizing factor, such as has been postulated in hydroa aestivale and similar conditions and in pellagra. Abnormal sensitivity to light seems to be for the most part on a genetic basis, although experiments with photosensitive dyes and drugs have shown that changes in reaction may be brought about by these agents.

The author seems to understand thoroughly this field of investigation, and his evaluation of evidence is convincing. The book may be highly recommended to any one whose interest runs along these lines.

Introduccion a la puericultura. By Dr. S. I. Bettinotti. Price, none given. Pp. 77, with 1 map. Buenos Aires: A. Frascoli, 1940.

This book, written in Spanish, was primarily intended for use in Argentina, but it should prove interesting to readers in other countries as well. All of the usual procedures for the care and training of infants and children and for the

establishment of proper hospitals and clinics to care for them are considered. Comparative figures for population and for deaths in the various sections of Argentina for the years between 1914 and 1934 are indicated on a map. This book presents a concise and practical pediatric program for a nation.

Schizophrenia in Childhood. By Charles Bradley, M.D. Price, $2.50. Pp. 136, with no illustrations. New York: The Macmillan Company, 1941.

This is a good discussion of the signs and symptoms of schizophrenia (dementia praecox) in children. The material for the book was obtained from an exhaustive survey of the literature and from extensive observations by the author on a small series of cases over a period of years. The chief value of the book lies in the critical analysis of the literature and in the bringing together of the meager collection of facts which make up the present day knowledge of this mental condition in children.

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Nederlandsche Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Piace: Pediatric Clinic, University Bratislava. Time: Six times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Av. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Richard M. Smith, 66 Commonwealth Ave., Boston.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Statler Hotel, Boston. Time: Oct. 9-11, 1941.
Region I. Place: Philadelphia.
Region III. Place: Cleveland.
Region IV. Place: Los Angeles.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.
Place: Brockville, Ontario. Time: June 14, 1941.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385-24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.
Place: Vancouver, B. C. Time: June 21, 1941.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. D. C. Darrow, 789 Howard Ave., New Haven.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Orville Barbour, 331 Fulton St., Peoria.
Secretary: Dr. Craig Butler, 715 Lake St., Oak Park.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1941.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. J. C. Iwersen, 236 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Greene, 910 Grand Concourse, New York.
Secretary: Dr. F. E. Chick, 2325 University Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. Philip Rosenblum, 2376 E. 71st St., Chicago.
Secretary: Dr. A. L. Newcomb, 1791 W. Howard St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Robert J. Mason, 460 Birmingham Rd., Birmingham, Mich.
Secretary: Dr. J. Hugh Lewis, 2966 Biddle Ave., Wyandotte, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. R. P. Schowalter, 411 E. Mason St., Milwaukee.
Secretary-Treasurer: Dr. George H. Wegmann, 2650 W. Hopkins St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Secretary: Dr. Alfred Langmann, 108 E. 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. Harold Flanagan, 711 Lowry Medical Arts Bldg., St. Paul, Minn.
Secretary-Treasurer: Dr. George B. Logan, Mayo Clinic, Rochester, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barba, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Louise Fry Galvin, 214 S. Boulevard, Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.